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# Systematic review of $\beta$ blocker, aspirin, and statin in critically ill patients: importance of severity of illness and cardiac troponin

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## ABSTRACT

Non-cardiac critically ill patients with type II myocardial infarction (MI) have a high risk of mortality. There are no evidence-based interventions to mitigate this risk. We systematically reviewed the literature regarding the use of medications known to reduce mortality in patients with cardiac troponin (cTn) elevation due to type I MI ( $\beta$  blockers, statin, and aspirin) in studies of critically ill patients without Type I MI. All PubMed publications between 1976–2/19/16 were reviewed. Search terms included:  $\beta$  blocker or aspirin or statin and intensive care unit (ICU) or critically ill or sepsis; 497 primary references were obtained. Inclusion criteria were as follows: (1) study population consisted of critically ill patients in the ICU with non-cardiovascular illnesses, (2) mortality end point, (3) severity of illness (or injury) was measured, and (4) the antiplatelet agent was primarily aspirin. Retrospective investigations, prospective observational studies, meta-analysis, systematic review, and randomized controlled trials were included; case reports were excluded. 25 primary references were obtained. The data were extracted and tabulated using data collection headings as follows: article title, first author/year/reference number, study type/design, population studied, outcome and intervention, and study question addressed. Evidence was not graded as the majority of studies were non-randomized (low-to-moderate quality). 11 studies were found through bibliography reviews for a total of 36 references. In conclusion,  $\beta$  blockers, statins, and aspirin may play a role in reducing mortality in non-cardiac critically ill patients. Benefit appears to be related to severity of illness, for which cTn may be a marker.

## INTRODUCTION

Critically ill patients are defined as those having an acute impairment of one or more vital organ systems such that there is a high probability of imminent or life-threatening deterioration in condition.<sup>1</sup> Despite significant resources provided for the treatment of the critically ill patients in the intensive care unit (ICU), the short-term mortality rate remains high.<sup>2,3</sup> Elevated serum cardiac troponin (cTn) is a common finding in this population, including those patients who do not initially present as cardiac emergencies, with 61% prevalence in patients with sepsis alone.<sup>4</sup> Serum cTn is often

measured to ‘rule out’ coronary arterial plaque rupture—or type I myocardial infarction (MI)<sup>5</sup>—as a cause for observed hypotension, arrhythmias, or chest pain in the critically ill patients, since treatment with urgent revascularization of the obstructed artery would be recommended.

Obstructive coronary disease, however, is not often found in critically ill patients with cTn elevation.<sup>6,7</sup> Rather, cTn elevation in this setting is thought to be due to myocardial oxygen supply/demand mismatch, categorized as a type II MI.<sup>5,8</sup> In this context, it is not uncommon for patients to lack the signs and symptoms caused by plaque rupture which either may not be present or may be masked by sedation or the underlying illness (figure 1). Importantly, even in the absence of obstructive coronary disease, elevated cTn correlates with the severity of illness and is an independent predictor of death,<sup>4,6,9–25</sup> although not all studies support this conclusion.<sup>26–30</sup> To further complicate the situation, comorbidities such as hypotension, renal failure, or sepsis increase the risk of coronary intervention which, if performed, may cause more harm than benefit.

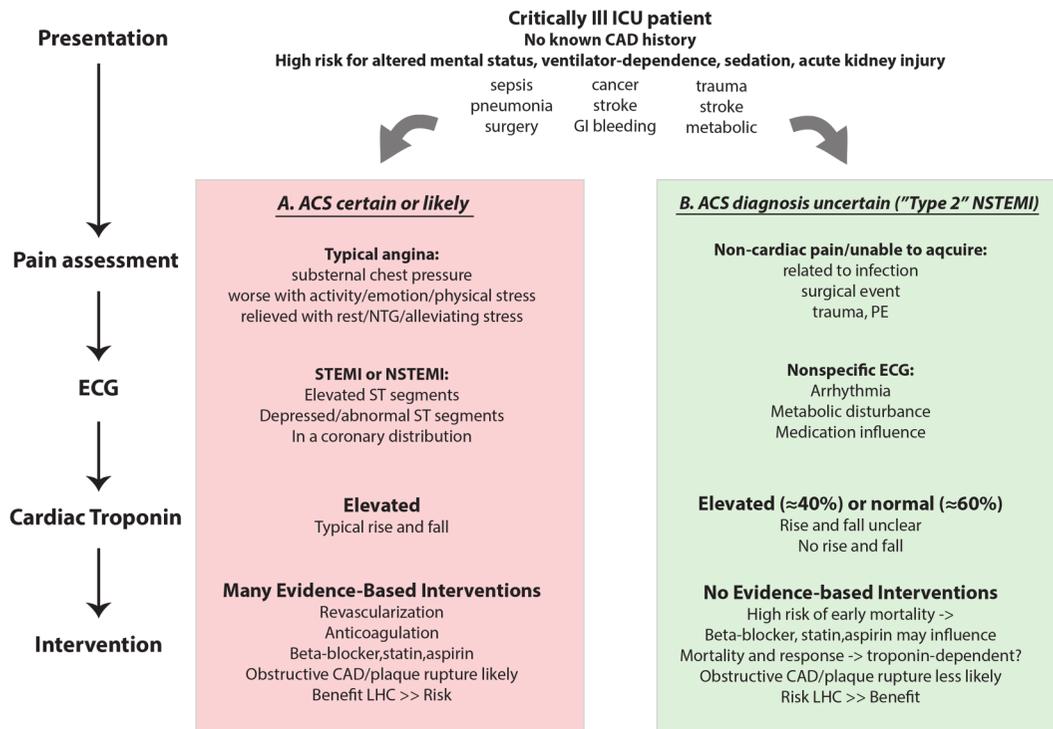
While the existing literature is robust regarding interventions and treatments known to reduce mortality for patients who present with type I MI, it lags behind in identifying interventions that reduce mortality in critically ill patients with type II MI and no prior coronary disease, despite the elevated mortality risk in this group. A common strategy has been to treat with  $\beta$  blockers, statin, and aspirin while the patient recovers, assuming that obstructive coronary disease is present, and then pursue testing for coronary disease once the patient has stabilized (figure 1). Early mortality reduction with  $\beta$  blockers, aspirin, or statin may provide a window of opportunity for subsequent evaluation and treatment of clinically significant coronary disease once the patient has stabilized from the underlying illness and the risks of intervention are mitigated.

This strategy has not been tested prospectively in critically ill patients with type II MI because there is little data in the literature to show benefit. To address this gap in knowledge, our group performed a retrospective study that included nearly 20,000 medical and surgical



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**Figure 1** Assessment of the critically ill patient with troponin elevation. There is a lack of evidence-based interventions in high-risk critically ill patients with troponin elevations and no (or uncertain) acute coronary syndrome (ACS). ICU, intensive care unit; CAD, coronary artery disease.

patients who were admitted to Veterans Administration Medical Center ICUs from 2007 to 2008.<sup>31</sup> Our data revealed two important findings: (1) that cTn level correlated with the severity of illness, and (2) there was a 30-day mortality reduction in patients taking aspirin,  $\beta$  blockers, and/or statins in a troponin-dependent fashion. Aspirin and/or  $\beta$  blocker use was associated with a 30-day mortality reduction, but only if cTn levels were high ( $\beta$  blockers: OR=0.80 (0.68, 0.94),  $p=0.0077$ ; aspirin: OR=0.81 (0.69, 0.96),  $p=0.0134$ ). The 30-day mortality was reduced in patients taking statins, but only if there was no or mild elevation of cTn (OR=0.66 (0.53, 0.82),  $p=0.0003$ ).

To the best of our knowledge, there is only one other report that demonstrated treatment benefit from medical intervention in a troponin-dependent fashion (see the 'Results' section).<sup>11</sup> Given the correlation between serum cTn and severity of illness that has been replicated in many studies, we extended our search to examine the impact of  $\beta$  blockers, aspirin, and statins in a critically ill population in which the severity of illness was also documented. Since  $\beta$  blockers and aspirin were associated with reduced mortality in patients who had high cTn but not in those with normal or intermediate levels of cTn, we hypothesized that  $\beta$  blockers and aspirin would also be associated with reduced mortality in patients with a comparably high severity of illness. Likewise, since statins were associated with reduced mortality in critically ill patients with normal or intermediate levels of cTn, we hypothesized that we would see a mortality benefit in critically ill patients with lower severity of illness.

This is of great importance for several reasons. First, there are no known interventions that reduce mortality in

critically ill patients with type II MI, a group at high risk of early death. Second, critically ill patients without cTn elevation may still benefit from statin use. All critically ill patients, therefore, may have mortality benefit from treatment with  $\beta$  blocker, aspirin, or statins.

The goal of this systematic review is to determine whether there is a literature base to support additional investigation of clinical treatment pathways using  $\beta$  blockers, statins, and/or aspirin in critically ill patients based on cTn or, in the absence of cTn levels, the severity of illness.

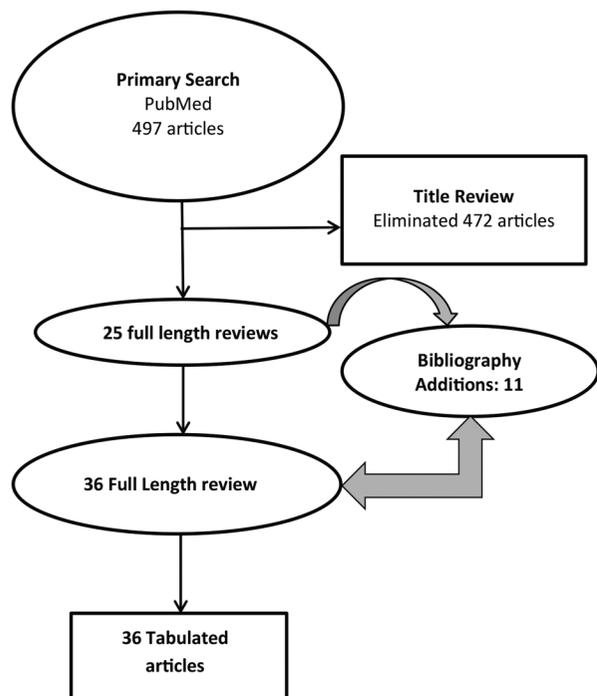
## METHODS

### Data source and searches

Literature searches were performed using PubMed February 19, 2016 and included the literature through 1976.

### Study selection

Titles were scanned and abstracts reviewed using exclusion and inclusion criteria following PRISMA-P guidelines.<sup>32 33</sup> Search terms included:  $\beta$  blockers or aspirin or statin and ICU or critically ill or sepsis; 497 primary references were obtained. Inclusion criteria were as follows: (1) study population consisted of critically ill patients in the ICU with non-cardiovascular illnesses, (2) mortality end point, (3) severity of illness (or injury) was measured, and (4) the antiplatelet agent discussed was solely (7 studies) or largely (3 studies) aspirin. All languages were included. Retrospective investigations, prospective observational studies, meta-analysis, systematic review, and randomized controlled trials were included; case reports were excluded. Thirty-six primary references were obtained (figure 2).



**Figure 2** Methods: process of review. Literature reviewed.

### Data extraction and quality assessment

The data were extracted and tabulated using data collection headings as follows: article title, first author and year, study type/design, population studied, outcome and intervention and study question addressed. Evidence was not graded as the majority of studies were non-randomized.

### Data synthesis and analysis

The articles were obtained in full length and read by two independent reviewers (FGR and MBC). Eleven additional studies were found through bibliography reviews for a total of 36 references.

## RESULTS

### Aspirin and antiplatelet agents

Systematic review of the literature investigating the role of aspirin in critical illness suggests a potential benefit in patients who are more severely ill (see online supplementary table S1). Mechanisms of benefit may be related to coagulopathy, coagulopathy being associated with increased organ failure and death.<sup>34</sup> Furthermore, organ failure contributes cumulatively to mortality.<sup>35</sup> Therefore, interrupting the coagulation cascade has been examined as a method to limit organ failure in many investigations with different agents. Data regarding the antiplatelet agent aspirin are robust, but largely retrospective. None of the literature discussed here measured cTn, however investigators measured and adjusted for the severity of illness or injury, in the case of critically injured trauma patients. The data suggest that aspirin may mitigate development of acute lung injury,<sup>36–40</sup> acute respiratory distress syndrome,<sup>36 41</sup> systemic inflammatory response syndrome,<sup>42</sup> and mortality,<sup>37 42 43</sup> but these investigations need to be confirmed in appropriate prospective clinical trials.

The largest investigation of aspirin in the critically ill is a propensity-matched retrospective study of 7945 patients at risk for SIRS, APACHE II Score 17–18 (1445 patients in each group; this APACHE II Score predicts a mortality of 26–30%).<sup>42</sup> Aspirin users had a significantly reduced mortality compared to non-users (10.9% aspirin users vs 17.2% non-users, HR 0.43,  $p < 0.001$ ), with benefit also in the sepsis-only group (27.4% aspirin users vs 42.2% non-users, 95% CI –18.8% to –8.6%). An APACHE II score of 17–18 is consistent with the report from Poe *et al*,<sup>31</sup> in which the patients who benefitted from aspirin use had a 30-day mortality of 30%, as well as the highest cTn. This supports the proposal that selected critically ill patients with a high severity of illness score may benefit the most from aspirin use.

Another retrospective, propensity-matched investigation of 1149 critically ill patients with high severity of illness (APACHE II 25–29, predicted mortality >50%) found that prehospital use of aspirin was associated with a decreased risk of acute respiratory distress syndrome (ARDS) (multivariate-adjusted OR, 0.659; 95% CI 0.46 to 0.94;  $p = 0.023$ ),<sup>41</sup> but only a trend towards decreased mortality in aspirin users (OR 0.697; 95% CI 0.47 to 1.03,  $p = 0.075$ ). Although other medications were recorded,  $\beta$  blockers as a class were not separately analyzed. Given the high risk of mortality in this patient population, it is possible that  $\beta$  blocker administration confounded this result. Similarly, in a study of patients with severe sepsis,<sup>39</sup> reduced incidence of ARDS/acute lung injury (ALI) was observed in the antiplatelet-treated group (OR 0.5, 95% CI 0.35 to 0.71,  $p < 0.001$ ), but no mortality benefit was demonstrated (OR 0.73, 95% CI 0.46 to 1.16),  $p = 0.19$ ).<sup>39</sup> In this investigation, APACHE III scores (55–57) are associated with an anticipated mortality of ~15–20%, which would correlate to the ‘intermediate cTn’ group of Poe *et al*, a cohort that did not have an associated mortality benefit with aspirin. Once again, severity of illness may be predictive of outcome with aspirin use.

A substudy of the prospectively enrolled Glue Grant found benefit from aspirin.<sup>37</sup> High-risk trauma patients who received transfusions (a risk factor for postinjury pulmonary dysfunction) were enrolled. Of 839 patients, 128 patients were on antiplatelet agents; 66% aspirin alone, 20% ‘other’ antiplatelet agents, and 14% received aspirin and another antiplatelet agent. Despite the fact that patients on antiplatelet agents were older, had more comorbid illnesses and were more severely injured, patients on antiplatelet agents had significantly less multi-organ failure and lung dysfunction with a non-significant trend towards decreased mortality.

A retrospective study of 979 septic patients (mean APACHE II score 22–23,  $p = 0.16$ ) showed mortality benefit from aspirin.<sup>44</sup> Logistic regression analysis determined that being on aspirin or a non-steroidal anti-inflammatory agent (NSAID; ibuprofen, diclofenac, or indomethacin) was associated with decreased mortality (aspirin (ASA) OR 0.57, 95% CI 0.39 to 0.83, NSAID OR 0.5, CI 0.26 to 0.94); however, being on both agents eliminated the benefit of either agent (ASA and NSAID OR 1.12, CI 0.55 to 2.25), indicating that NSAID use must be considered in clinical trials.

Even patients with severe gastrointestinal bleeding may have a mortality benefit with aspirin. A total of 717 patients admitted for non-variceal upper gastrointestinal

bleeding from 1993 to 2010 were studied.<sup>45</sup> The primary outcome was in-hospital mortality. Despite the fact that patients on ASA only were older and had more comorbidities, multivariate analysis showed that being on ASA only was an independent predictor of reduced in-hospital mortality (OR 0.26, 95% CI 0.13 to 0.53,  $p=0.0002$ ).

A propensity-matched study of 3855 patients investigating aspirin use in patients at risk for acute lung injury found no benefit from aspirin (OR 0.67; 95% CI 0.44 to 1.01,  $p=0.055$ ); however, the APACHE II score was relatively low, between 9 and 12 (approximate mortality risk 15%).<sup>38</sup> The reduced benefit may have been related to the reduced risk in this cohort. A retrospective study of mixed admissions to medical and surgical ICUs supports this assertion.<sup>46</sup> Patients with an APACHE II score of 21 or greater had a significant benefit from antiplatelet pretreatment as compared to patients with lower APACHE II scores. Severity of illness, or cTn levels if they are indeed a biomarker of severity of illness, may need to be considered when prescribing aspirin.<sup>31 37</sup>

One nested cohort trial of 763 ICU patients (20% receiving aspirin) combined results from two RCTs and showed potential harm from aspirin therapy.<sup>47</sup> The authors did not provide a mechanism for this difference as compared with considerable literature showing benefit, rather they highlighted the need for prospective, randomized investigation.

In summary, systematic review of a series of large, retrospective studies of critically ill patients suggests that aspirin provides clinical benefit, particularly when the severity of illness is high, although this finding is not uniform. This supports the need for prospective, randomized, controlled investigations of aspirin in the critically ill, with careful evaluation of the possible role of severity of illness and troponin positivity.

### Statins

Statins hold promise in the treatment of sepsis, primarily via immunomodulatory and anti-inflammatory mechanisms.<sup>48</sup> Systematic review of the literature describing statin use in the critically ill revealed a confusing story, but one that may be clarified by addressing severity of illness. Observational cohort investigations, retrospective and prospective, have demonstrated a potential benefit of statins in patients with sepsis,<sup>49</sup> but the bulk of data from prospective, randomized, blinded, placebo-controlled trials suggests otherwise.<sup>50–53</sup> The remainder of this discussion will focus on results from prospective randomized-controlled trials and their meta-analyses.

The conclusion from recent systematic reviews and meta-analyses is that there is insufficient evidence to support the use of statins to derive a mortality benefit in patients with severe sepsis.<sup>54–57</sup> A total of 1894 patients were involved in randomized, blinded, and controlled clinical trials of statin therapy in sepsis. Primary outcome was 28-day mortality,<sup>50</sup> in-hospital mortality,<sup>51</sup> number of ventilator-free days for a maximum of 28 days,<sup>52</sup> hemodynamic parameters,<sup>58</sup> and IL-6 levels.<sup>53</sup> None of the trials showed mortality benefit except in patients who were prior users of statin (Kruger;  $n=77$  patients, OR 0.17 (0.03 to 0.85),  $p=0.03$ ).<sup>53</sup> Patients in these trials had a high severity of illness, with approximate APACHE II scores ranging from 19 to 25 and estimated mortality rates between 30%

and 53%. It was concluded that severely septic patients do not benefit from statin use, although it is not clear if prior use impacts mortality.<sup>53</sup>

Severity of illness may play an important role in determining whether a patient will benefit from statins, as suggested by a large retrospective cohort analysis<sup>31</sup> and one randomized, controlled, double blind study.<sup>31 59</sup> Among 16,208 critically ill patients with a severity of illness comparable to APACHE II score of 14 or less, logistic regression analysis showed that patients taking statins had an associated 30-day mortality benefit (OR 0.66; 95% CI 0.53 to 0.82,  $p=0.0003$ ).<sup>31</sup> Patients with a higher severity of illness (equivalent to APACHE II score  $>19$ ) did not have an associated mortality benefit with statin use (OR 0.99 (95% CI 0.82 to 1.19),  $p=0.91$ ). This retrospective study could not adjust for prior statin use, however. It is possible that the entire effect observed may be related to prior statin use rather than severity of illness.

A randomized, placebo-controlled, double blind investigation of statin use in septic patients on the ward showed that 40 mg of atorvastatin in statin-naïve patients prevented conversion of sepsis to severe sepsis (4% vs 24%,  $p=0.007$ ).<sup>59</sup> The mean APACHE II score for this group correlated to an anticipated mortality rate of 15%.

This systematic review of prospective, randomized, controlled studies of statins in the critically ill suggests that statin use may benefit patients who are less severely ill on admission, supporting an immunomodulatory effect beneficial at early stages of illness. The impact of prior use of statins also needs to be clarified. It is possible that most benefit derives from prior use, but at least one randomized trial of septic ward patients suggests that statin-naïve patients may benefit, as well.

### $\beta$ blockade

Systematic review of the literature reveals that  $\beta$  blockade may reduce mortality in critically ill patients who are more severely injured or ill, or who have higher cTn levels on admission. Only one prospective, randomized, placebo-controlled clinical investigation of the impact of  $\beta$  blockade on mortality in the critically ill has been published.<sup>60</sup> A total of 154 patients who presented with hemodynamically unstable septic shock requiring norepinephrine were investigated. After careful resuscitation, the patients randomized to treatment were given intravenous esmolol. The primary outcome was a reduction in heart rate to 80–94 bpm and maintained for 96 hours, which was achieved; the mean reduction in heart rate in the esmolol group was 18 bpm ( $p<0.001$ ). Surprisingly, at 28 days, the esmolol group had a mortality rate of 49.4%, whereas the control group was 80.5% ( $p<0.001$ ). The authors pointed out that historically, patients with the highest heart rates were most at risk of death<sup>61–65</sup> and hypothesized that perhaps the highest risk patients would benefit most from  $\beta$  blockade.

Several prospective observational studies suggest  $\beta$  blockers may reduce mortality in patients with traumatic brain injury (TBI). A non-randomized, prospective, observational study of 440 TBI patients was performed in which propranolol was given within the first 24 hours of ICU admission at the discretion of the trauma or neurosurgery attending doctors.<sup>66</sup> Propranolol—a non-cardioselective  $\beta$  blocker—was chosen based on a retrospective

investigation of 1755 TBI patients which showed that there was no in-hospital mortality benefit from  $\beta$  blockade in general (427 patients, multivariable analysis OR 0.85, 95% CI 0.536 to 1.348). However 78 propranolol users (18%) alone had significant mortality benefit (OR 0.199, 95% CI 0.043 to 0.92) despite being more severely injured.<sup>67</sup> In the prospective observational investigation, propranolol use was independently associated with reduced early mortality (OR 0.25 (0.08, 0.74,  $p=0.012$ )).<sup>66</sup> A second prospective observational study of propranolol use with 38 moderate-to-severe TBI patients (28 propranolol group, 10 control patients) supported its safety, but did not show a mortality benefit (10% vs 10.7%,  $p=0.9$ ).<sup>68</sup> This may reflect the fact that 80% of patients in the non-propranolol group had been given other forms of  $\beta$  blockade during their admission. Clearly, additional high-quality prospective investigations are necessary to show benefit of  $\beta$  blockade in TBI patients as well as investigating the importance of cardioselectivity; however, this early work indicates that there is little harm. Support for lack of harm and possible benefit in TBI patients also comes from considerable retrospective work,<sup>69–72</sup> all of which suggests that  $\beta$  blockade has a protective effect despite higher risk injuries.

$\beta$  blockade also appears to show mortality benefit in critically ill non-TBI trauma patients.<sup>11 73 74</sup> Martin *et al*<sup>11</sup> investigated the role of cTn elevation in 1081 trauma patients and asked whether  $\beta$  blockers and aspirin impacted outcomes. Consistent with the majority of similar investigations, the authors found increased mortality in trauma patients who also had elevated cTn (29% of patients with elevated cTn, mortality 16% in cTn negative vs 44% in cTn positive groups, OR 3.0,  $p<0.01$ ). APACHE II score was an independent predictor of mortality ( $p=0.001$ ). Seven per cent of patients were administered  $\beta$  blockers, primarily to patients with elevated cTn (11% vs 6%,  $p=0.01$ ).  $\beta$  blocker use was associated with a 50% reduction in mortality, but only in the group with elevated cTn (cTn elevated: 38% vs 16%,  $p<0.01$ , cTn not elevated: 14.3% vs 16%,  $p=0.77$ ). Adjusting for multiple factors still resulted in a strong mortality benefit (OR 0.50; 95% CI 0.24 to 1.02,  $p=0.057$ ). This is consistent with the work of Poe *et al*,<sup>31</sup> which showed similar benefit across the critical illness spectrum in patients with high cTn as compared to patients with normal or mildly elevated levels.

Considerable retrospective work shows an association with  $\beta$  blockade and reduced mortality in the non-traumatic critically ill. A large propensity-adjusted cohort study used Denmark's prospective, population-based medical database.<sup>75</sup> Thirty-day mortality was measured in 8087 ICU patients taking  $\beta$  blockers prior to admission as compared to non-users. Similar to other studies, despite the fact that  $\beta$  blocker users were older and had more comorbid diseases than non-users, there was significant association of mortality benefit with cardioselective agents (OR 0.70; 95% CI 0.58 to 0.83). A retrospective cohort study comparing heart-rate lowering agents in patients admitted to the ICU in acute respiratory failure showed no mortality benefit among 188 chronic obstructive pulmonary syndrome (COPD) patients.<sup>76</sup> This population, however, had a severity of illness (APACHE II 19–20) that may have also benefited from aspirin use, if the work of Poe *et al*<sup>31</sup> is accurate. Mortality benefit, therefore, may have been

masked by aspirin use which was not addressed in this study.

Additional retrospective cohort studies of non-critically ill patients with COPD support the safety of  $\beta$  blockade.<sup>77–79</sup> Three investigations showed early mortality benefit with  $\beta$  blocker use in non-critically ill patients with COPD<sup>77 78</sup> or respiratory arrest.<sup>79</sup> The majority of benefit was seen in patients with cardiovascular disease in a study of non-critically ill COPD patients<sup>78</sup> and respiratory arrest patients.<sup>79</sup> When patients with cardiovascular disease are excluded, a mortality benefit remained, adjusted HR 0.68 (95% CI 0.46 to 1.02).<sup>77</sup>

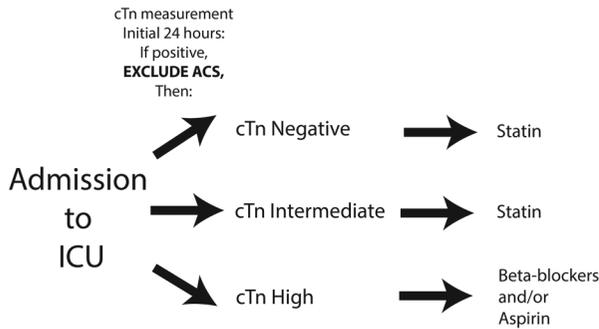
## SUMMARY AND CONCLUSIONS

Reasonable conclusions that can be cautiously extracted from this systematic review are as follows:

1. Cardiac troponin levels may be a biomarker for severity of illness and multiorgan failure, thus providing a potential method to rapidly identify those patients at greatest risk of death for whom  $\beta$  blockers and aspirin may have the greatest benefit.
2. Aspirin appears to reduce acute lung injury, occurrence of ARDS, and may also impact mortality in critically ill patients. The most severely ill may obtain the most benefit. This needs to be tested in prospective, randomized, blinded, and controlled investigations.
3. Prospective, randomized, and controlled investigations show that statins appear to have no benefit in reducing mortality or illness in severely septic patients. Some data suggest overall safety in septic patients. This impacts patients who have other indications for statins, such as cardiovascular disease. Close surveillance of liver and muscle biomarkers is recommended due to the potential for liver and muscle dysfunction in the severely ill.
4. Conclusions cannot yet be drawn regarding the benefits of statins in less severely ill patients. In this population, statins may reduce the severity of illness and may have a mortality benefit, but this also needs to be confirmed with appropriate prospective interventional trials.
5. In the one prospective, randomized, controlled study of  $\beta$  blockers in adequately resuscitated septic patients,  $\beta$  blockers appear to have significant mortality benefit, although there has not yet been such an investigation designed with a mortality end point. It is possible that cardioselectivity may be important, although esmolol (cardioselective) and propranolol (non-selective) have shown mortality reduction in small studies of patients with sepsis and TBI, respectively. Side-by-side prospective studies of both classes of  $\beta$  blocker would be necessary to address this question.
6. All medications must be recorded and considered in future studies of critical illness.

This systematic review cumulatively suggests that statin therapy may provide immunomodulatory benefits at early stages of illness before multiorgan failure develops, whereas aspirin and  $\beta$  blockers may reduce mortality in the sickest of patients for whom platelet aggregation, microvascular obstruction, and organ dysfunction may occur.

A treatment pathway that needs to be tested prospectively is summarized in figure 3. Potentially, all non-acute coronary syndrome (ACS) admissions to the ICU would



**Figure 3** Measurement of cTn in critically ill patients may help guide potentially life-saving therapy. Consideration for assessment of patients with type II myocardial infarction. Modified from Poe *et al.*<sup>31</sup>

trigger a baseline cTn measurement that could guide appropriate medical management. After excluding the possibility of ACS and assessing patient-specific risks and benefits, it is possible that the addition of  $\beta$  blockers, statins, and/or aspirin would reduce mortality in critically ill patients depending on the severity of illness, a surrogate marker being the admission cTn level. Prospective, observational studies addressing these questions must be developed.

**Contributors** FGR, MBC, HJ and RHV-P have all contributed to the conception or design of the work, in revising this work critically for important intellectual content, have all contributed to the final version and have all agreed to be accountable for all aspects of the work.

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