# WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

**Worksheet author(s)**

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<tr>
<th>Name</th>
<th>Date Submitted for review</th>
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<td>Hans-Richard Arntz</td>
<td>6/18/2010</td>
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## Clinical question.

In patients with suspected ACS/MI in prehospital and emergency department settings (P), does the use of statins (I), compared with standard management (i.e. no prehospital and emergency department use of statins) (C), improve outcome (e.g. infarct size, EKG resolution, survival to discharge, 30/60 d mortality) (O)?

This worksheet addresses in intervention/therapy.

This worksheet is a revision of an existing worksheet.

## Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

## Search strategy (including electronic databases searched).

Search in Medline, AHA Endnote Master library, Embase and Cochrane library using the text words acute coronary syndrome (STE and NSTEMI), myocardial infarction, unstable angina, statin(s), pravastatin, simvastatin, atorvastatin, fluvastatin, rosuvastatin, and lovastatin resulting in a total of 2242 hits.

Also some review articles published in high ranked journals were searched for additional publications.

## State inclusion and exclusion criteria

- Duplicates, double publications, non-systematic reviews, letters, animal studies, comments and articles without available abstract were excluded.
- Also studies which started treatment clearly later than 24 hrs after the index event/hospital admission were excluded. Studies, however, which started treatment in some pts immediately after index event/admission were included even if other pts were included somewhat later within the first few days (see also reviewers comments)

## Number of articles/sources meeting criteria for further review:

Finally 177 abstracts were reviewed and 36 articles fulfilled the criteria for further review and were included in the evidence based review.
# Summary of evidence

## Evidence Supporting Clinical Question

| Good | {Hulten, 2006}\(^{E2}\) \(^{C}\)  
{Patti, 2007}\(^{E1}\) | {Bauer, 2009}\(^{B}\)  
{Kinlay, 2003}\(^{E3}\)  
{Olsson, 2007}\(^{E2}\)  
{Saab, 2004}\(^{E1}\), \(^{E2}\)  
{Waters, 2002}\(^{E3}\) | {Heeschen, 2002}\(^{C}\), \(^{E4}\) | {Chan, 2003}\(^{E1}\), \(^{E2}\)  
{Cuculi, 2008}\(^{C}\), \(^{E2}\)  
{Daskalopoulou, 2008}\(^{C}\)  
{Fonarow, 2005}\(^{C}\), \(^{E1}\)  
{Lenderink, 2006}\(^{C}\)  
{Saab, 2006}\(^{E}\)  
{Spencer, 2004}\(^{C}\), \(^{E1}\) | {Cahoon, 2007}\(^{E1}\)  
{Ebrahimi, 2008}\(^{E3}\) |
|---|---|---|---|---|
| Fair | {Gonzalvez, 2004 p 916}\(^{E3}\)  
{Nagay Hernandez, 2008 p 379}\(^{E}\)  
{Nakamura, 2008 p 365}\(^{E}\)  
{Wright, 2002 p 1085}\(^{E2}\) | {Bybee, 2001}\(^{B}\), \(^{E4}\)  
{Bybee, 2004}\(^{E3}\)  
{Kanadasi, 2006}\(^{E1}\), \(^{E2}\), \(^{E3}\)  
{Sakamoto, 2006}\(^{E2}\)  
{Shal'nev, 2007}\(^{E3}\)  
{Thompson, 2004}\(^{E2}\) | | {Kiyokuni, 2009}\(^{E}\)  
{Wright, 2006}\(^{B}\), \(^{E1}\), \(^{E3}\) | {Chyrchel, 2006}\(^{E3}\)  
{Hara, 2007}\(^{E3}\) |
| Poor | {Kayikcioglu, 2002}\(^{E2}\)  
{Teshima, 2009}\(^{E}\) | | | | |

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### Level of evidence

- **A** = Return of spontaneous circulation
- **C** = Survival to hospital discharge
- **E** = Other endpoint
- **B** = Survival of event
- **D** = Intact neurological survival
- **E1** = Short term (at discharge or 30 days) MACE
- **E2** = Long term mortality and MACE
- **E3** = Cardiac markers (and short term MACE)
- **E4** = non fatal MI

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*Italics = Animal studies*
### Evidence Neutral to Clinical question

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<td>{Newby, 2002} E2</td>
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### Evidence Opposing Clinical Question

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REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Some specific difficulties arose in selection of the studies evaluated resulting in the following decisions:
Some investigations allowed inclusion/randomization lasting from “immediately after admission” up to several days after the index event. These studies were included into the worksheet in contrast to those where study inclusion started not before several days after the index event/admission. The same procedure was selected in evaluating metaanalyses i.e. those investigations were evaluated which included studies with early inclusion within the first 24 hrs after admission the index event/admission.

There is no study investigating prehospital or systematic emergency department use of statins in ACS patients. However, the review of evidence resulted in an overwhelming amount of data supporting early (intensive) statin treatment (< 24 hrs of admission) in a wide variety of patients presenting with all forms of an ACS i.e. STEMI, NSTEMI and UAP. Early intensive statin treatment is not only supported by reduced mortality and MACE rates including stroke at least on a long term view but also during short term course as shown in large registries, and also by data from the short term course of surrogate parameters as for example reduction of inflammatory markers or biomarkers of myocardial damage.

Data are in favour of treatment in all specific subgroups i.e. the elderly, females and diabetics. There is no specific data relating to different reperfusion treatments. However supporting evidence exists showing advantages for preprocedural initiation of statin treatment with regard to course of cardiac markers and clinical events in patients undergoing percutaneous coronary intervention. Finally it may be concluded from the available literature, that any preexisting statin treatment should not be interrupted but continued in case of hospital admission.

Acknowledgements:
Martina Weiland for preparing the manuscript.

Citation List


Registy data on outcome of 6358 pts hospitalized with an non-STEMI ACS of whom 1247 were treated with statins before hospitalisation and 5111 were not on statins. CK release was significantly lower with pre-treatment; PCI and CABG rate was not different between groups. After adjustment for several risk factors including history of coronary heart disease, renal impairment and diabetes, in hospital mortality with statin pretreatment was 35 % lower (95 % CI 0.46—0.9).
LOE2 Supporting good


Metaanalysis on 12 randomised controlled trials involving 13024 pts with ACS (STEMI and Non-STE-ACS). Treatment was started within 14 days (1-14 days) after the index event. The analysis shows a trend to less periods of unstable angina but not in the primary endpoint of this study i.e. the combination of death, MI or stroke. Serious adverse events were rare (a search strategy is published in the Cochrane database for systematic reviews).
LOE1 Neutral good


Further analysis of registry data in which 66 pts with AMI receiving statins within 24 hrs after admission were compared with matched pairs (n=198) regarding CK release, showing that early treatment results in lower peak CK release.
LOE2 Supporting fair

Registry data on a small group of AMI pts (n=66) treated with statins within 24 hrs after admission with a group of matched pairs (n=198) not receiving statins. Study resulted in less death and re-MI in the statin group.
LOE2 Supporting fair


Metaanalysis on effects of preprocedural statins before PCI including 1 retrospective analysis, 4 prospective observational studies and 3 randomised controlled trials mostly in pts with elective PCI (bedside the ARMYDA ACS study (Patti et al) with different endpoints and varying observational periods (24 hrs to 21 months) suggesting a reduced amount of myocardial necrosis post PCI with preprocedural statin
LOE 5 Supporting good


Registry data on pts with urgent and elective PCI on influence of statins on hs-CRP levels and clinical outcome. Patients with statin pre-treatment had lower hs-CRP levels and less periprocedural MI's irrespective of cholesterol levels. Pre-procedural hs-CRP levels remained an independent predictor of cardiac mortality and MI's within 1 year only for pts not treated with statins. After propensity adjustment statin treatment was associated with a marked reduction in mortality in pts with high hs-CRP levels (5.7 % vs 14.8%, p=0.009) (statin treatment may therefore indicated specifically in the subgroup of pts with high hs-CRP levels.
LOE 4 Supporting good


Observational study in 140 consecutive non STE-ACS pts who had pre-PCI treatment with 80 mg atorvastatin or not (groups not differ in relevant characteristics). During follow-up the rate of MACE (death, MI or re-PCI did was significantly lower with atorvastatin pre-treatment (25.9 % vs 8.1 %) as was the rate of death and MI (18.8 % vs 2.3 %)
LOE5 Supporting fair


Registry data on in-hospital outcome of 11603 pts presenting with ACS subdivided in those with chronic and continued statin therapy, initiation of statins at hospital admission and those who never had statins neither before admission nor until discharge. Patients on continuing statin treatment or initiation of statins at admission had fewer MACES and a lower in-hospital mortality irrespective of risk groups e.g. the elderly renal impairment, diabetes etc.
LOE 4 Supporting good


Registry data showing that discontinuation of statins in pts with STEMI may cause increased mortality at 1 year if compared to pts who never used statins, new statins starters, and those who continued with statin treatment. A specific cause however (e.g. very ill pts) for discontinuation of statins could not be excluded and may play a role for worse outcome in this group.
LOE4 Supporting good


Metaanalysis of 2 prospective randomized and 4 retrospective studies investigating the protective effect of statin pre-treatment on the rate of myocardial infarction post-PCI showing that statin treatment reduces the rate of post
procedureal MI rates and tends to reduces the MACE rate up to 12 months.

LOE 5  Supporting  good


Registry data from the NRMI registry on 17118 AMI pts who were treated with statin and continued at admission 21978 who started statin within 24 hrs of admission 126128 pts who did not receive early statin treatment and 9411 pts pts whose statin therapy was discontinued. New or continued treatment with a statin in the first 24 hours was associated with a decreased mortality compared with no statin use (4.0% and 5.3% compared with 15.4% no statin). Discontinuation of statin treatment was associated with a slightly increased mortality (16.5%). Early statin use was also associated with a lower incidence of cardiogenic shock, arrhythmias, cardiac arrest, rupture, but not recurrent myocardial infarction. Propensity analysis yielded mortality odds ratios of 0.46 for continued therapy, 0.42 for newly started therapy, and 1.25 for discontinued therapy for matched pairs versus no statin therapy (all p values <0.0001).

LOE 4  Supporting  good


Randomized investigation on 71 pts with STEMI receiving very early (< 10 hrs from symptom onset) 40 mg pravastatin or not with regard to inflammatory markers (CRP and IL-6) showing a decrease in CRP but not IL-6 with pravastatin already within 7 days compared to no or delayed treatment.

LOE1  Supporting  fair


Non randomised study in 87 NSTE-ACS patients who had an LDL-cholesterol of 100 mg/dl or less and were undergoing PCI. The study compares those who were on statins with those who were not pretreated before PCI. Patients with statin pre-treatment revealed lower levels of CK-MB and TNT (measured 6 hrs after PCI) even if pre-PCI levels of these parameters showed no difference. However, there was no difference in MACES (death, MI, CHF or target lesion revascularisation) within 6 months.

LOE 5  Supporting  good


Retrospective analysis of the PRISM trial analyzing outcome in patients with no statin treatment after admission, discontinuation of statins and continuing statins at admission. This study shows that discontinuation of statins results in more clinical events (death and non-fatal MI) compared to no statin at all, whereas the group with continued statin treatment had the lowest event rate of all groups.

LOE3  Supporting  good


Metaanalysis on 13 randomised controlled trials on 17963 ACS pts comparing early intensive statin treatment with placebo/usual care with regard to mortality and adverse cardiovascular events. This analysis results in fewer deaths and cardiovascular events beginning after 4 months of treatment and during the later course.

LOE 1  Supporting  good


Non randomized study comparing the effect of atorvastatin started within 24 hrs vs no statin treatment in 102 ACS pts on hsCRP and plasma amyloid A (SAA) levels 5 days and 6 months after the event as well as clinical outcome. Marker levels were reduced already within 5 days. Clinical outcome including congestive heart failure during index hospitalisation and unstable angina, rate of heart failure and need for revascularisation within 6
months after discharge were less frequent with early statin treatments. LOE2 Supporting fair


Small study on 77 STEMI pts initially treated with thrombolysis of whom 40 received 40 mg pravastatin immediately with the lytic. Later on a PCI was performed. Compared to controls the rate of recurrent angina as well as the MACE rate was significantly lower (32.5 %) vs 75.6 % p= 0.0001 in controls during 6 months. LOE2 Supporting poor


Substudy on 2402 pts of the randomized myocardial ischemia reduction with aggressive cholesterol lowering (MIRACL) study, showing that CRP and serum amyloid A but not interleukin-6 (trend only) was significantly reduced with 80 mg atorvastatin, started within 24-96 hrs of hospital admission in the whole spectrum of pts presenting with all forms of ACS. LOE 2 Supporting good


Registry data on outcome of 39 pts with STEMI receiving fibrinolysis who had statin-pretreatment, compared with 271 pts who had no statin pre-treatment. Before consecutive PCI TIMI flow did not differ between groups, but after PCI TIMI grade III flow rate was higher with statins and AUC for CK was lower with statins. LOE4 Supporting fair


A registry data from the European Heart Survey on statin naïve pts with STEMI and Non-STE-ACS receiving statins within 24 hrs after hospitalisation (n=1426) or not (n=6771). Pts with early treatment showed a significantly reduced (0.4 % vs 2.6 % at 7 days (adjusted HR 0.34 95 % CI 0.15-0.79)) and 30 day mortality also after adjustment for a propensity score and other established risk factors. Data for NSTE-ACS pts were similar to those of STEMI pts. LOE 4 Supporting good


Registry data on 210 pts with ACS divided into a group of pts receiving statins within 2 days of admission compared with those with initiation of treatment > 2 days. There was no difference in clinical outcome (composite of death, recurrent angina requiring hospitalisation, Re-Mi, revascularisation or stroke). LOE4 Neutral fair


Small randomized study comparing “conventional” or treatment with rosuvastatin (40 mg) with respect to surrogate markers for endothelial function (oxidative stress and nitric oxide). Nitric oxide levels decreased with conventional treatment but increased with rosuvastatin, whereas oxidative stress was higher after 7 days in both groups. LOE1 Supporting fair


Small randomized study using a specific IVUS technique comparing the development of carotid plaque
vulnerability and inflammatory biomarkers in ACS patients with pitavastin or placebo. Compared to placebo plaques were more intensely stabilized and levels of CRP, VEGF and TNFα were lower with pitavastin within one month of treatment.

LOE1 Supporting fair


Retrospective observational study on pts with NSTE-ACS-STEMI from the SYMPHONY trial with statin treatment beginning up to 7 days after the ACS event. The analysis revealed different outcomes regarding death and MI related to total and LDL cholesterol levels at start of treatment with a trend to worse outcome in pts with cholesterol levels beyond 150 mg/dl (LDL cholesterol 124 mg/dl) respectively for death and 237 mg/dl total cholesterol (207 mg/dl) LDL cholesterol respectively ) for death and MI respectively. Higher cholesterol levels tended to result in better outcome with early statin treatment.

LOE 4 Nutral  good


Substudy of the MIRACL-study showing that in the elderly (> 65 years) with early atorvastatin treatment within 24-96 hrs of admission a similar treatment effect can be achieved as in younger patients (the risk of an event being 2-3 times higher in the older group!)

LOE 2 Supporting good


Relatively small sized randomized placebo controlled study on 171 pts with NSTE-ACS receiving 80 mg Atorvastatin 12 hrs before PCI: Pre-treatment with atorvastatin reduced the 30 days incidence of the primary endpoint (death, MI or unplanned revascularisation): Incidence 5 % with Atorvastatin, 17 % with placebo (p=0.01) mainly by reduction of the incidence of MI (5 % Atorvastatin, 15 % placebo) (MI defined as > 2 times ULN of CK-MB)

LOE 1 Supporting good


Comparison of 1284 ACS pts (UAP and NSTEMI and STEMI) receiving statins within 24 hrs of admission with 355 pts treated later then 24 hrs. A multivariate logistic regression model taking a wide variety of risk factors into account resulted in less episodes of in hospital heart failure, lower incidence of cardiac arrests and cardiogenic shocks with early statins as well as the composite of death, re-infarction and stroke during hospital stay, compared with pts treated later. This effect was not more present after 6 months.

LOE2 Supporting good


Registry data on 774 elderly pts (>65 years) with ACS receiving statins within 24 hrs of admission (n=611) or later (n=163). Episodes of heart failure were less frequent with statins during hospital stay but there was no difference regarding death, re-MI or stroke during hospitalisation.

LOE4 Supporting good


Randomized placebo controlled study on 486 pts with normal cholesterol levels, presenting with an acute myocardial infarction (69 % STEMI). Treatment with any statin (or no statin) was initiated within 96 hrs of AM and follow up duration lastest up to 24 months. The event rate (cardiovascular death, non fatal AMI, recurrent
ischemia, CHF or stroke) was 6.1% with a statin and 11.4% without (p=0.0433). Specifically the rate in CHF was lower with statins (p=0.0154 and p =0.0264 respectively) and recurrent ischemia. Kaplan Meier estimates for events started to diverge about 3-4 months after initiation of treatment.

LOE2 Supporting fair


Small study (108 pts with ACS) looking for the effect of 40 mg simvastatin in addition to "standard treatment" vs standard treatment alone" started within 24 hrs after admission with regard to course of CRP levels and incidence of angina periods for 6 months. The study shows more pronounced fall in CRP level at 6 months and significant lesser incidence of periods of angina in pts with simvastatin.

LOE2 Supporting fair


Registry data from NSTEMI pts of the NRMI registry of whom 9001 had statin treatment before hospitalisation which was continued within 24 hrs after admission, 4870 pretreated pts with discontinuation of statin treatment and 54635 pts who never had statins. With discontinuation of statin treatment rate of death, heart failure, shock, VF/VT was 12.5% vs 4.9% in those with continued statin treatment. Also with discontinuation a slightly increased event rate compared to those who never had statins was observed. Moreover pts with continued treatment had fewer events compared to those who never had statin treatment. These results remained principally unchanged after adjusting for numerous confounders and applying a propensity score.

LOE4 Supporting good


Small randomized study on 30 pts with AMI and PCI who received low dose (10 mg) atorvastatin within 48 hrs after admission. Controls received no statin. Ventricular function measured by echocardiography was better with atorvastatin. Also BNP and ANP levels were significantly lower with atorvastatin.

LOE2 Supporting poor


Early terminated randomised placebo controlled study on treatment with 20 – 40 mg pravastatin within 24 hrs of onset of symptoms in 3408 pts (planned 10000) with all forms of ACS, resulting in a trend in favour of pravastatin with regard to the primary endpoint i.e. the composite of death, MI or re-admission to hospital within 30 days or randomisation (event rate 11.6% vs 12.4% p =0.48). Treatment proved to be safe.

LOE2 Supporting fair


Substudy of the MIRACI trial showing that the incidence of stroke is halved (1.6% vs 0.8%) within 16 weeks of intensive cholesterol lowering therapy with atorvastatin (initiated 24-96 hrs after admission) compared to placebo in pts presenting with ACS.

LOE2 Supporting good


Metaanalysis on 4 small trials of the total of 12 studies also reviewed in the Briel et al paper. This analysis also results in a neutral or discrete positive trend (interpreted as due to the lack of power of these studies) in favour of statin treatment.

LOE 1 Supporting fair

Registry data on 220 pts suffering an AMI who were treated with statins within 24 hrs of hospitalisation compared with 3006 pts who received no statins or were treated later. Early treatment resulted in lower mortality (2.7 % vs 9.2 %), lower peak CK and a lower CHF rate compared to delayed or nor therapy.

LOE4 Supporting fair