QUESTION

Should aspirin be given early or prehospital vs late or in-hospital for adult non-traumatic chest pain? (FA586)	
PROBLEM:	What is the feasibility of first aid providers administering oral aspirin to adults with non-traumatic chest pain (early administration)? Does this influence survival, the incidence of cardiac arrest and what are the potential clinical complications?
OPTION:	Early or first aid administration of oral aspirin
COMPARISON:	Late or in-hospital administration of oral aspirin
MAIN OUTCOMES:	Survival, complications, cardiac arrest
SETTING:	First aid setting, adults with non-traumatic chest pain
PERSPECTIVE:	
BACKGROUND:	Chest pain is a common symptom in adults resulting in more than 8 million visits to emergency departments (EDs) each year in the US (Rahko, 2014,59) and is most commonly an early symptom of myocardial infarction. Administration of oral antiplatelet agents has improved survival and has become a recommended routine standard of care for chest pain in emergency care (Tayeb 2011, 7; ISIS2 1988, 349). Given that aspirin is a common and a cheap treatment, readily available in society, we investigated whether it is feasible and beneficial for first aid providers to initiate antiplatelet therapy in the pre-hospital phase by administering aspirin shortly after the onset of chest pain (early administration) rather than waiting until arrival at hospital (late administration).
CONFLICT OF INTEREST:	Authors declared they have no conflict of interest.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ◉ Yes ○ Varies ○ Don't know	Out of the 8 million adults yearly visits to an ED in the US due to chest pain, about one million have acute coronary syndrome (ACS) and a third have myocardial infarction (MI) (O´Gara, 2013, 128). In adults with non-traumatic chest pain, early treatment with antiplatelet agents might be crucial in the management of MI (Tayeb 2011 7). Oral aspirin, a cheap and readily available antiplatelet agent, could be administered by first aid providers or self-administered early after onset of non-traumatic chest pain and potentially improve survival from MI.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	For the critical outcome survival at 7 days, 30 days and 1 year we found a benefit for early over late administration.	

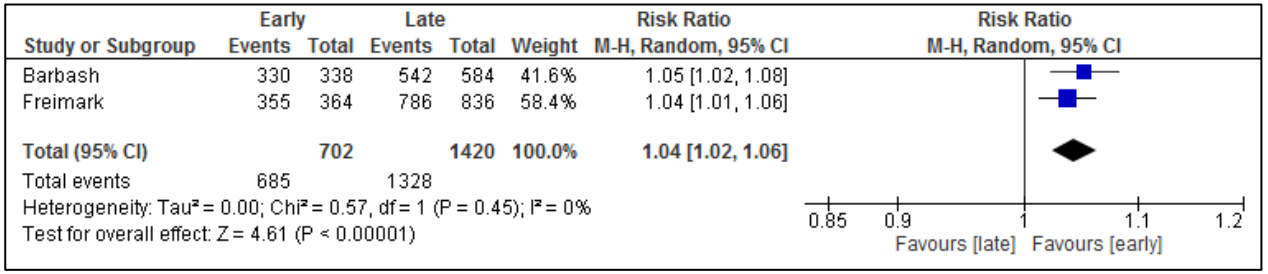

Figure 1. 7 days survival

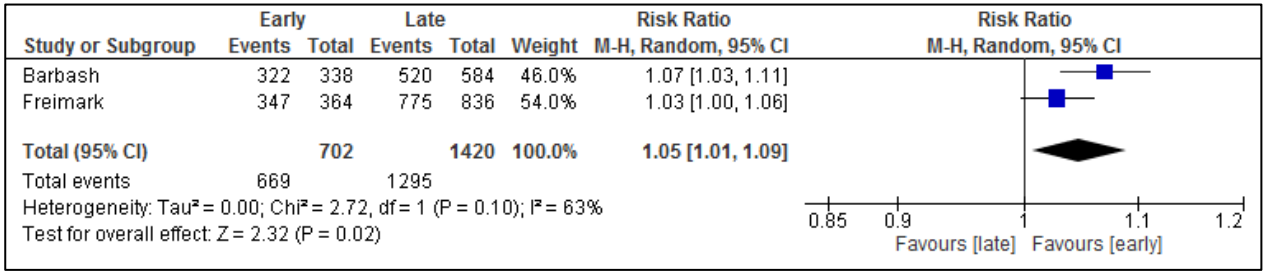

Figure 2. 30 days survival

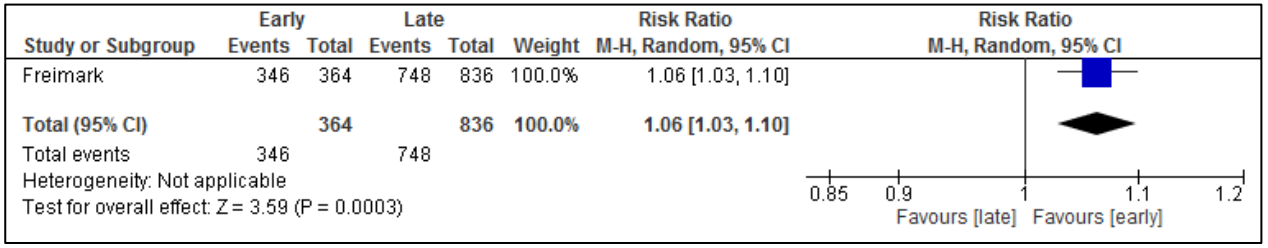

Figure 3. 1 year survival

There was no significant difference for early compared with late administration for survival at 35 days.

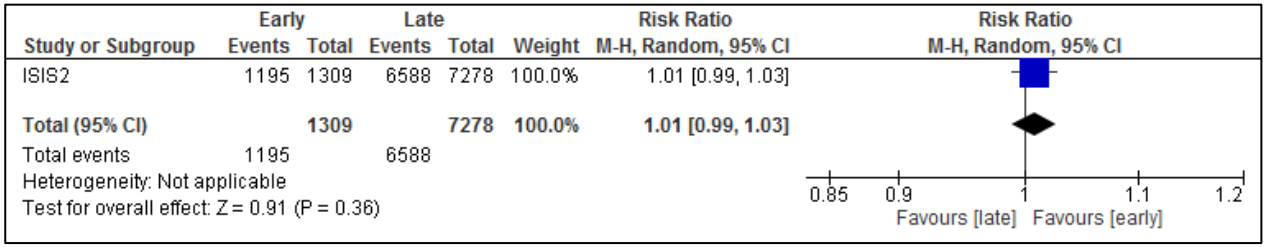

Figure 4. 35 days survival

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	For the critical outcome complications we found no-significant difference between early versus late administration.	No included studies reported incidence of cardiac arrest. However, the FATF decided that some of the reported 'complications' could be interpreted as cardiac arrest since they would, in a clinical situation, be associated with a cardiac arrest. The FATF felt that the two studies could not be combined due to heterogenicity between them. It was not clear what patients in cardiac arrest received CPR and which did not (disparity in numbers between those reported in cardiac arrest and those that received resuscitation)

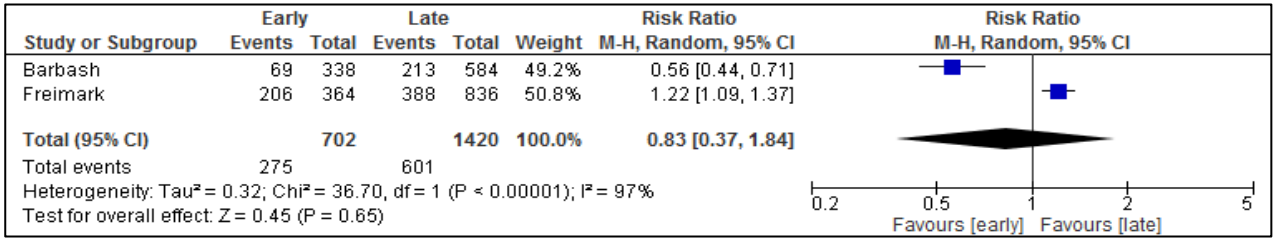

Figure 5. Complications

For the critical outcome incidence of cardiac arrest we found conflicting results in two studies showing increased risk in one study (Freimark 2002 381) and non-significant difference as well as decreased risk (two different measures was used) in another study (Barbash 2002 141).

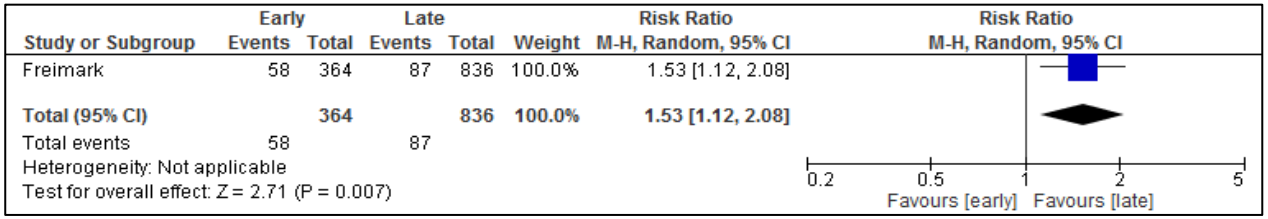

Figure 6. Cardiac arrest Freimark 2002 381

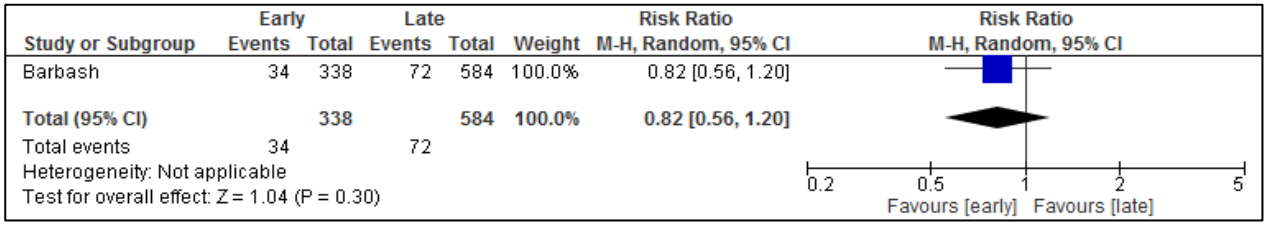

Figure 7. Cardiac arrest Barbash (measure 1/2- asystole, primary VF, sustained VT)

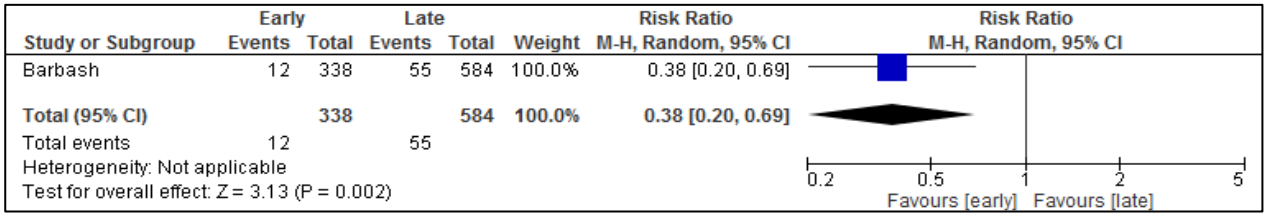

Figure 8. Cardiac arrest Barbash (measure 2/2- resuscitation)

Freimark 2002 381: Ventricle tachycardia (VT)/Ventricle fibrillation (VF).

Barbash 2002 141: Two separate analyses were performed since resuscitation was reported as a complication but it was unclear if it was a generic term for resuscitation or if it includes performing CPR. The overlap between those needing resuscitation and having the dysrhythmias associated to a cardiac arrest in a clinical situation was not reported

1.Asystole, primary VF, sustained VT

2.Resuscitation

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	There are limitations in study design and imprecision. All included studies were performed some 20 to 30 years ago and even though the cohort population and exposure might be comparable to care of today, the outcome of a MI has considerably improved since the studies were performed. Aspirin is now an established part of routine care of MI care and the Task Force believes that it is unlikely that any new RCTs will be performed on aspirin administration for the management of MI.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The Task Force considered that there is no important uncertainty or variability as to the value of the main outcome, survival.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Survival is ranked as critical outcome and the FATF considered that survival most likely for most people has high priority. The undesirable effects show conflicting results and the increased incidence if cardiac arrest, namely ventricle fibrillation/ventricle tachycardia in hospital, in one study did not affect survival within the same study.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ◉ Large savings ○ Varies ○ Don't know	We were unable to find any formal studies on cost-effectiveness. Oral aspirin is a non-prescription drug in most countries and is readily available from several pharmaceutical companies. Cost per tablet differs between countries but it is likely to be less than 1 USD per tablet.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No identified studies assessed costs.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ◉ No included studies	The cost for the intervention and comparison are the same but the cost for the tablet might be paid by the first-aid provider or patient compared to being paid for by the hospital and/or patient. The FATF discussed that the cost of one tablet of aspirin (approximately 1 USD) which was considered acceptable for a person willing to provide first aid if the critical outcome of improved survival could be achieved.	

Equity

What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	In Europe and in Asia there are restrictions as to whom or how a non-prescription drug can be administered by a first aid provider (a non-health care professional). This could affect who can administer aspirin in a first aid setting. It was felt that where these restrictions exist, first aid providers might encourage the patient to self-administer aspirin themselves with the assistance of the first aid provider.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	The intervention is probably acceptable to all key stakeholders. First aid providers in countries with prescribing restrictions might be able to develop guidelines that would allow for them to encourage self-administration of oral aspirin tablets.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Oral aspirin tablets are readily available and easy to carry in first-aid kits. However, the recommended dose may vary from country to country depending on national guidelines. First aid provision may need to include awareness of the requirement for self-administration in countries where prescription regulations could limit the administration of aspirin by health care ´professionals only.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the option	Conditional recommendation against the option	Conditional recommendation for either the option or the comparison	**Conditional recommendation for the option**	Strong recommendation for the option
○	○	○	●	○

CONCLUSIONS

Recommendation

For adults with non-traumatic chest pain we suggest the early administration of aspirin as a first aid intervention compared with late, in-hospital, administration of aspirin (weak recommendation, very low certainty evidence).

Justification

This PICO was prioritized for review by the First Aid Task Force based on:

a) the likelihood of encountering a person with non-traumatic chest pain in a first aid setting
b) the administration of oral aspirin as being a simple, safe and readily available intervention for first aid use
c) the potential for increased survival from early administration of aspirin in the event of a myocardial infarction

The current CoSTR has the same recommendation as the CoSTR 2015.

In making these recommendations, the First Aid Task Force considered:

- We recognize that although we identified the population of interest to be adults with symptoms of non-traumatic chest pain in the first aid setting, the included evidence is considered indirect as it was limited to adults with suspected MI and not all causes of non-traumatic chest pain
- We place a higher value on the benefits of aspirin, such as survival from a MI, which outweigh the possible risks identified in one study (Freimark 2002 381), i.e. an increased risk of ventricle tachycardia or ventricle fibrillation in-hospital not influencing survival, and the adverse effect of minor bleeding identified in ISIS 2 and described in a 2015 CoSTR (Singletary 2015 S269)
- We were not able to perform meta-analysis of all three included studies even though they report survival outcomes at relatively similar times (30 days and 35 days). The FATF discussed the possibility that these studies may have included different populations (suspected MI versus ST-segment elevation AMI), different doses of administered aspirin, have different study designs (cohort versus RCT) and also that the studies were performed at different chronological times (1988 versus 2002) where clinical practice, for example reperfusion therapy, has changed both the management and outcomes of the illness
- We recognize that all included studies were performed about two to three decades ago and that even if the population and exposure might be comparable the care offered today, the outcome of MI has improved
- The Task Force felt that it was unlikely that any major new studies will be performed on this topic considering the cost effectiveness of the simple administration of aspirin
- First Aid guideline groups will need to consider that prescribing practices in Europe and Asia might require self-administration for first aid, rather than direct administration of aspirin by a first aid provider due to national, regional, state or provincial regulations
- The Task Force discussed concerns about first aid providers being able to differentiate chest pain of cardiac origin from other causes of chest discomfort. The term non-traumatic was added to the descriptor to enhance and simplify the clinical signs and the differential diagnosis of chest pain possibly related to the onset of a myocardial infarction. However, with any treatment recommendation using a symptoms-based approach such as chest pain, the task force expressed a consensus opinion that it is very important that first aid educational materials clearly indicate what signs and symptoms the first aid provider should look for. Furthermore, that the absolute contraindications for the administration of aspirin (i.e, allergy or active bleeding) be emphasized. Guideline organizations may also want to consider including additional first aid behaviors appropriate for their geographic locations, such as activating emergency medical services

Subgroup considerations

None

Implementation considerations

Europe and Asia have prescribing restrictions. This may affect who can directly administer aspirin in a first aid setting. In such countries it may be possible for first aid providers to encourage self-administration rather than directly providing and administering the tablet themselves.

Monitoring and evaluation

None

Research priorities

Current knowledge gaps include but are not limited to:

- Is aspirin safe if given to patients with non-traumatic chest pain of all etiologies, i.e. not only suspected MI?
- What is the time critical window for the effective administration of aspirin in adult patients with acute myocardial infarction?
- What is the minimal effective dose for the oral administration of aspirin for non-traumatic chest pain in adults?
- What formulations of aspirin should be used in the first aid setting (i.e. enteric coated tablets, uncoated tablets)