ARC SAC SCIENTIFIC REVIEW
Aspirin for Chest Pain

Question:
Should the American Red Cross teach First Aid and CPR providers / rescuers to administer aspirin in the setting of chest pain suspected of being a heart attack?

Overview:
The incidence of heart attacks in the United States is one per 1000 population per year. Chest pain is a major manifestation of heart attacks. There has been popular press and advertising attention rendered to the common medical practice of administering aspirin in the setting of chest pain thought to be of cardiac origin. Thus it is very important that Red Cross First Aid personnel be advised on the implementation of this therapy which has been shown to be of benefit in the early response to heart attacks. Aspirin is a safe and effective treatment for heart attacks in combination with many other methods of care.

Literature Search:
A search of the literature was completed in 2001 The results of these studies were critically appraised for applicability to the question of efficacy and low complication rates for aspirin use. A second literature search was conducted of MEDLINE in 2006, using the keywords: aspirin and heart attack, myocardial infarction and stroke.

Several comprehensive reviews of the use of aspirin in cardiovascular disease along with scientific statements by the American Heart Association and the American Stroke Association were consulted.

Triennial 2012 Literature Search
The review of literature was limited to PubMed using the following parameters-
1. “Aspirin AND myocardial infarction AND mortality”;
2. “Acute myocardial infarction AND aspirin”;
3. "Aspirin AND acute myocardial infarction AND prehospital"; and
4. “Aspirin AND pre-hospital”

Inclusion criteria were limited to-
1. Human subjects
2. Randomized controlled trial, controlled clinical trial
3. Available abstract
4. Published in the English and published within the last 5years. The last 3 or 5 five years was selected to avoid overlapping with the 2010 American Heart Association and American Red Cross Guidelines for First Aid[1] and BLS guidelines.[2]

The initial search yielded-
1. 54 articles using the key terms “Aspirin AND myocardial infarction AND mortality.”
2. One-hundred and fifty seven articles were identified using the key terms “Acute myocardial infarction AND aspirin.”

3. Four were identified using the key terms “Aspirin AND acute myocardial infarction AND pre-hospital"
4. Three articles were identified using the key terms “Aspirin and pre-hospital.”

Of these articles-
1. 6 articles using the key terms “Aspirin AND myocardial infarction AND mortality.”
2. One-hundred and fifty seven articles were identified using the key terms “Acute myocardial infarction AND aspirin.”
3. Zero articles were identified using the key terms “Aspirin AND acute myocardial infarction AND pre-hospital"
4. Three articles were reviewed using the key terms “Aspirin and pre-hospital.”

In situations where an article referred a possible source, the abstract and/or article was located and reviewed at www.pubmed.com.

Triennial 2015 Literature Search

((((chest pain) AND acute coronary syndrome)) AND ((aspirin OR ASA))) AND ((("first responder*" OR "paramedic*" OR "lay responder*" OR "first aid provider*" OR "Emergency Medical Services"[Mesh] OR "Emergency Responders"[Mesh]))) Filters: Randomized Controlled Trial retrieved 3 articles [below]
[w/o RCT retrieved 39]

Dracup 2009 - intervention vs. control group, population were patients at risk of CAD/ACS, mostly males age 67 >80% followed by a cardiologist
Intervention was education on ACS symptoms, taking ASA, call 911
Education increases the rate of ASA use, as well as time to 911; there were no differences in mortality
NO significant side effects were reported

Fuchs 2010 - impact of providing 250 mg ASA IV on arrival at the ER - not related to our question

Bhattacharya 2010 - tirofiban for ACS - not appropriate for our question

2 ("chest pain") AND ("first responder*" OR "paramedic*" OR "lay responder*" OR "first aid" OR "Emergency Medical Services"[Mesh] OR "Emergency Responders"[Mesh]) AND aspirin
Filters: Humans; English

3 (undifferentiated) AND ("chest pain*") AND ("first responder*") OR "paramedic*" OR "lay responder*" OR "first aid" OR "Emergency Medical Services"[Mesh] OR "Emergency Responders"[Mesh])
AND Humans[Mesh] AND English[lang] [w/o/aspirin]

Barron 2013 - A study of implementing a protocol, not the effects of ASA use, outcomes on survival - this study showed that EMDs can use a protocol and more patients get ASA - no data on safety, outcomes, etc.

Takakuwa 2010 - a review of the characteristics of patients with chest pain that got ASA in an ED, not a first aid perspective - not applicable

Colwell 2009 - review of an EMS systems adherence to a protocol for medics to give ASA to patients - not applicable

Whyte 2008 - financial motivators for medics to give ASA - not appropriate

Martínez-Sellés 2008 - risk stratification with ECG and Troponin - not appropriate

Seferovic 2006 - tamponade, not ASA for ACS

Herlitz 2006 - a review of current treatments, not appropriate

Hooker 2006 - a review of why EMTs do not provide ASA - common is that a) the medics didn't believe it was ischemic pain and b) licence issues — this study shows that ECG and higher level risk stratification are needed to identify all cases of chest pain - and that basic symptoms may miss some presentations - no adverse reactions listed

Meischke 2006 - education of seniors about the benefits of calling 911 for chest pain - not appropriate

McVaney 2005 - review of paramedics use, and descriptions of why they didn't use ASA - 54% of ACS patients in this 2457 patient study got ASA. 79% of people who got nitroglycerin for ACS also got ASA [21% of patients who got nitroglycerin did not get ASA]. This shows that EMTs — and perhaps first aid providers — need more education on the benefit of ASA from outcomes vs. the use of NTG for symptoms [no outcome benefit] - interesting but no direct outcomes

Rittenberger 2005 - looked at reasons for delay of transport in EMS system - not directed related to ASA

Quan 2004 - a review of 25,600 ambulance cases, looking specifically for adverse events 0 none were found - ASA can be given safely out of hospital - helpful

Stoykova 2004 - results of a protocol for ambulance use of ASA - effect of implementing the protocol, not of the ASA

Snider 2004 - also a study of the results of a protocol implementation

Bledsoe 2003 - general review

Woolard 2001 - benefits of audits in ambulance system to improve ASA use - not appropriate

Rothrock 2001 - gender inequality in ASA use - more commonly given to men vs. women by EMS systems

Herren 2001 - general review article

Brown 2000 - demographic factors affecting call 911 vs. delaying care - not appropriate

Weaver 1993 - prehospital fibrinolysis

Bland 1993 - prehospital fibrinolysis

S1 ("paramedic*" OR “lay responder*” OR “first aid” OR “Emergency Personnel" OR "Emergency Responders" OR “lay public”) AND (chest pain AND undifferentiated) AND Aspirin
0 results

S2 ("paramedic*" OR “lay responder*” OR “first aid” OR “Emergency Personnel" OR "Emergency Responders" OR “lay public”) AND chest pain AND Aspirin
47 results chose 13 removing duplicates from Pubmed search

S3 (chest pain AND undifferentiated) AND Aspirin
11 results

Selected 9

Figgis 2010 - review of paramedics compliance - not applicable

Tataris 2015 - review of EMS use from database - effects of a protocol - not relevant

Woolard 2001 - review of paramedics adherence to a protocol

Yelaja 2001 - newspaper article

Ware 2012 - newspaper article

Elwood 2000 - ASA for prophylaxis in stroke, Alzheimers, ACS, and others - not appropriate

Osborne 2010 - newspaper article

Schlinkmann 2007 - newspaper article

Redd 2004 - ASA use within an hour of arrival in the ED improves survival vs. > 1 hours after arrival - reaffirms that early administration is better for ACS

Triennial 2018 Literature Search

Search 1

Among adults experiencing chest pain due to suspected myocardial origin (P), does administration of aspirin (I), compared with no administration of aspirin (C), change cardiovascular mortality, complications, adverse effects, incidence of cardiac arrest, cardiac functional outcome, infarct size, hospital length of stay (O)?

Search 1 PubMed

("chest pain") AND ("first responder*" OR "paramedic*" OR "lay responder*" OR "first aid" OR "Emergency Medical Services"[Mesh] OR "Emergency Responders"[Mesh]) AND aspirin
Filters: Humans; English and 2014-2017 3 results removing human did not change results

Search 2 PubMed

Search (undifferentiated AND "chest pain*") AND ("first responder*" OR "paramedic*" OR "lay responder*" OR "first aid provider*" OR "Emergency Medical Services"[Mesh] OR "Emergency Responders"[Mesh])
Filters: Publication date from 2014/01/01 to 2017/12/31; English
12 hits

Search 3 Onesearch

(("paramedic*" OR “lay responder*” OR “first aid” OR “Emergency Personnel" OR "Emergency Responders" OR “lay public”)) AND (aspirin AND chest pain) Limits: English, Publication date 2014 to 2017

9 four dups remov

PubMed, OVID - Medline, UI ONESEARCH
English, dates 2014-2017

20 results found

20 articles excluded.
Reasons: no outcome data, epidemiologic data only, not relevant to topic.
Hand search of references found 3 additional articles; 2 included, 1 excluded due to lack of relevance to the target population

Search 2:

Among adults receiving aspirin for chest pain due to suspected myocardial origin (P), does administration of enteric coated aspirin (I), compared with non-enteric coated aspirin (C), change time to systemic absorption, bioavailability, efficacy (O)?

Search 1
(("Enteric coated" OR "enteric coating" OR ("Tablets, Enteric-Coated"[nm]))) AND (absorption OR disintegration OR dissolution OR resistance OR bioavailability) AND aspirin
Filters: Publication date from 2014/01/01 to 2017/12/31; English 13 hits

Search 2
((enteric coated OR non-enteric)) AND aspirin 54
Filters: Publication date from 2014/01/01 to 2017/12/31; English

adding in 'chest pain' to either search was 0 hits

Search 3
Search related "Journal of pharmaceutical sciences"[Jour] AND 100[volume] AND 9[issue] AND 3884[page] AND 2011[pdat] Filters: Publication date from 2014/01/01 to 2017/12/31; English 15 hits

Search 4
Search related "Basic & clinical pharmacology & toxicology"[Jour] AND 116[volume] AND 212[page] AND 2015[pdat] Filters: Publication date from 2014/01/01 to 2017/12/31; English 17 hits

99 hits =73 after removing dups and not useful = 69

Same Search set run in IU OneSearch-multi-database
only 4 unique hits - highlighted in olive
73 total hits
There were very few hits for adding in both chest pain and aspirin
PubMed, OVID - EBM Reviews (Cochrane DSR, ACP Journal Club, DARE), UI ONESEARCH
2014-2017/Jul 18
English

73 articles reviewed, 73 excluded
Reasons: lack of clinical data, lack of pharmacokinetic data, not relevant to topic.
Hand search of references found 2 additional articles; 1 included, 1 excluded due to lack of comparative data.

Three total articles included in new review.[1,2,3]

Scientific Foundation:
Current literature supports the theory that unstable atherosclerotic plaques not only narrow vessels and retard blood flow but can rupture.
There is extensive evidence that aspirin has significant activity that interferes with the clotting actions of platelets. There is convincing data to support the use of aspirin to prevent myocardial occlusion and thus myocardial infarction both acutely and as a preventive measure. Studies have shown long-term aspirin therapy reduces the risk of coronary occlusive disease by as much as 25%. (1-3).

Aspirin has a rapid onset of action within 30 minutes. There is great therapeutic range and safety to aspirin use in the setting of acute ischemic chest pain patients. The risk of overdose is very low if two chewable baby aspirin tablets are stocked at a low level in personal first aid kits (two tablets, 81 mg each).
The acute coronary setting is accepted as being recognized if the lay rescuer notices that the patient displays:

- Chest pain or pressure (usually constant, heavy, squeezing)
- Shortness-of-Breath (air hunger, dyspnea)
- Sweating
- Weakness
- Radiation of unusual feelings or pain down the left arm or into the neck
- Nausea
- Fear of “impending doom”
- Change in the patient’s usual pattern of “Angina”

The "lay rescuer" should immediately call 9-1-1 or activate the local EMS unit; and make the patient as comfortable as possible.
If the patient is conscious and able to take oral medication and the patient denies

- Allergy to aspirin
- Stomach ulcer disease, or,
- Taking “blood thinners” (Coumadin, Warfarin, or other anti-platelet drugs)

the lay rescuer should offer two chewable (162 mg) baby aspirins or up to as much as one five grain (325 mg) adult aspirin tablet with a small amount of water.
If a patient has been revived or resuscitated from a suspected cardiac event, then the "lay rescuer" should offer aspirin treatment if the patient is able to ingest oral medications and does not have any of the above listed contraindications.

NOTE: Tylenol, Acetaminophen, Motrin, Advil, Ibuprofen and other pain killers are NOT equivalent to Aspirin. Combination and enteric-coated aspirin products are NOT supported by

this advisory because the literature does not contain studies of efficacy of these specific aspirin formulations in the acute chest pain setting.

Updated Scientific Foundation from 2012 Triennial Review
According the 2010 American Heart Association and American Red Cross Guidelines for First Aid it is difficult, even for the healthcare professional to differentiate patient experiencing chest discomfort of cardiac origin or from other chest discomfort.[1] Because of this it has been recommended that first aid providers assume that chest discomfort is cardiac in nature until proven otherwise. Cardiac chest discomfort is typically described as a "crushing" or "pressing" that is often accompanied by shortness of breath or perspiration. In some cases cardiac chest discomfort may not present with these classical characteristics, particularly in women. Thus standard of care requires immediate activation of EMS. It is recommended to not delay and not transport a patient yourself to a healthcare facility. While waiting for EMS to arrive, the "first aid provider may encourage the patient to chew 1 adult (not enteric coated) or 2 low-dose "baby" aspirin if the patient has no known allergy to aspirin or other contraindication to aspirin, such as evidence of a stroke or recent bleeding (Class IIa, LOE A).

Part 5 of the adult basic life support 2010 American Heart Association *Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care*[2] too stresses the importance in patient suffering from acute coronary syndrome (ACS) that Emergency Medical Dispatcher (EMD) and Emergency Medical Service providers must be trained to recognize ACS symptoms, even if atypical. They further states- "It is reasonable for dispatchers to advise patients with potential cardiac symptoms to chew an aspirin (160 to 325 mg), providing the patient has no history of aspirin allergy and no signs of active or recent gastrointestinal bleeding (Class IIa, LOE C).

Updated Scientific Foundation from 2015 Triennial Review
Review of 2015 ILCOR guidelines — references used were from 1979, 1988, 1990, 2001, 2002 and 2004 — no newer articles in their review either — ILCOR for public review indicate that ASA should be given for chest pain presumed to be cardiac in origin - the usual dose is 325 mg tablet, or 2-4 baby aspirin chewed

ASA remains useful for ACS [mortality benefit], although the ideal timing and appropriate undifferentiated population remains discussed. In patients with high probability of ACS< or proven ACS, ASA is helpful. The risk for ASA in undifferentiated patients appears exceptionally low, but is not zero.

What is missing is an understanding of the patient populations that has a significantly high probability of benefiting from ASA administration, rather then just for people with 'chest pain'. We recommend an ARC SAC FA review of signs, symptoms and risk factors of ACD that improves the sensitivity and specificity to the point that ASA benefit clearly outweighs the relatively low risk. On initial review, there are studies [eg Swap & Nagurney, JAMA Nov 23/30; 2005 - Vol 294, No 20, P2623] that will help inform on this.

Updated Scientific Foundation from 2018 Triennial Review

In 1979, Elwood and Williams[1] (LOE 1b) conducted a randomized controlled trial that evaluated the use of **aspirin on 28 day mortality** in patients with myocardial infarction. In this study researchers sent community practitioners who agreed to participate six sealed randomized envelopes containing either aspirin **300 mg or placebo**. Practitioners were instructed to give the intervention at first contact with a patient believed to have suffered a myocardial infarction. Follow up was completed by mail at one month with practitioners for subject details. The primary outcome was 28 day mortality. Infarction was determined as best judged by the practitioner. A total of 2530 subjects were enrolled, myocardial infarction was determined in 1705 patients who were used for analysis. There was no statistically significant difference in 28 day mortality in those treated with aspirin vs those treated with placebo (RR = 0.97; 95% CI 0.80-1.18). In those subjects who were treated within 4 hours of symptoms, again there was no difference in 28 day mortality in those treated with aspirin vs those treated with placebo (RR = 0.94; 95% CI 0.74-1.20). This study provided very low quality evidence, downgraded for bias, indirectness and imprecision. The authors concluded that this study provides no evidence that early aspirin intervention alters 28 day mortality in patients with myocardial infarction.

In 1990, Verheugt et al[2] (LOE 1b) conducted a randomized controlled trial that evaluated the use of early (onset < 12 hours) low dose aspirin (**100mg/day**) on infarct size and clinical outcome in 100 patients with anterior wall myocardial infarction. Patients were randomized to receive either **100mg** of plain aspirin or placebo per day. The initial dose was given within 12 hours of hospital admission along other treatments according to standard of care. Infarct size, as measured by cumulative serum lactate dehydrogenase (LDH), was the primary endpoint; death, re-infarction, unstable angina and revascularization were secondary endpoints. Three month follow up was completed in all patients. Early aspirin was not found to reduce the infarct size compared to placebo (1431 ± 782 U/L vs 1592 ± 1082 U/L; p = 0.35). Re-infarction occurred in one subject in the aspirin group versus six in the placebo group (p = 0.06). This study provided low quality evidence downgraded for indirectness and imprecision. The authors of this study concluded that early intervention with low dose aspirin does not significantly influence infarct size, but does decrease the re-infarction rate.

In 2011 Sai et al[3] (LOE 1b) published a randomized crossover trial to evaluate the characteristics of **buffered aspirin tablets** and **enteric coated aspirin tablets** when **chewed** or **not chewed** on aspirin pharmacokinetics and platelet aggregation in healthy human volunteers. In this study 12 healthy subjects ingested either intact or chewed buffered aspirin (BA) or enteric coated aspirin (EC) tablets (Bufferin 81mg or Bayaspirin 100mg) and blood samples were collected at intervals after tablet ingestion for analysis. Volunteers participated in each stage of the trial with a 2 week washout period between stages. Two volunteers withdrew before completion of the study leaving only some of their data available for analysis. Mean residence time (MRT), which is defined as area under the first moment curve divided by area under the curve was a mean of 1.9 hours (SD = 0.9 hrs) for BA and 6.8 hrs (SD = 1.3 hrs) for EC. Chewing EC tablets shortened the MRT to 2.4 hrs (SD =1.2 hrs). In this small sample size there was not a statistically significant difference between the MRT of intact or chewed BA versus chewed EC. Mean difference (MD): 0.05 hrs (95% CI = -0.4 – 1.4) for intact BA vs chewed EC; MD: 0.1 hrs (95% CI = -0.88 – 0.68) for chewed BA versus chewed EC. Intact and chewed BA as well as chewed EC inhibited platelet aggregation to a statistically significant degree by 20 minutes of ingestion, whereas it took unchewed EC 4 hours to attain this effect. This provided low quality evidence which was

downgraded for bias, indirectness and imprecision. The authors concluded that chewing EC aspirin greatly accelerated MRT and inhibition of platelet aggregation to a level comparable to that of intact and chewed buffered aspirin.

Recommendations and Summary of Triennial Reivew:
The 2018 triennial review did not find significant updates to the 2015 review. With the 2017 search only three additional articles were found pertaining to the PICO. While all were randomized trials, they have significant limitations and evidence quality was downgraded. As summarized above, neither the Elwood nor Verheugt articles demonstrate a benefit in early aspirin administration in either infarct size or mortality. However both articles provide low quality evidence and have significant limitations. In addition, the Verheugt[2] article uses a smaller dose of aspirin than what is current recommended in both first aid recommendations and in clinical practice. For these reasons it was not felt that the evidence was not compelling enough to change the 2015 Treatment Recommendations. Sai et al[3] demonstrated that chewed buffered aspirin and enteric coated aspirin have a similar onset time of platelet inhibition. Although this is low quality evidence, it provides further data that chewed enteric coated aspirin tablets can be used as an alternative to chewed regular release aspirin tablets or chewable aspirin tablets if these options are not available to the provider.

Regarding the overall recommendations, there is little data to determine the risks and benefits of aspirin administration by first aid providers. For this reason, the recommendation for administration by first aid providers is less certain and, therefore, there are no Standards, only Guidelines. Based on the available evidence, it is felt that the majority of literature suggests that the benefit of aspirin administration outweighs the risks in those patients without known contraindications. Therefore, first aid providers may provide aspirin to patients suspected of having a heart attack and who have no known contraindications. However, due to the lack of definitive data, if the diagnosis is uncertain, the first aid provider may choose not to administer aspirin and wait for EMS arrival or presentation to the hospital. Literature demonstrates comparably fast onset times of chewed aspirin, whether it be regular release or enteric coated aspirin. Therefore, if aspirin is administered, it should be chewed. As prior literature suggests that the optimal dose of aspirin in a heart attack is between 162 mg and 325 mg, we included this in the recommendations. While these three articles do not provide information that would change current American Red Cross Treatment Recommendations, we felt that we should clarify some wording of the 2015 document. We clarified that “low dose” aspirin is 81 mg and that 2 to 4 of these tablets can be given. We also clarified that an “adult” aspirin tablet is 325 mg. Due to these minor changes this results in a recommendation of “revise”.

Treatment Recommendations - Revise

Standards:

- None

Guidelines:

- It is reasonable for a first aid provider to provide ASA to a patient suspected of having a heart attack

- If there is uncertainty regarding the likelihood of a heart attack, it is reasonable to wait for the arrival of EMS
- The recommended dose of aspirin is 2 to 4 81 mg aspirin (162 -324 mg) or one 325 mg tablet (coated or non-enteric coated). The aspirin should be chewed.
    - Notes: Four, chewable, 81 mg tablets or one 325 mg non-enteric coated tablet should be included in First Aid Kits for use in the setting of acute chest pain.(FA KIT DOC)

Options
- None

Algorithm for Aspirin Use by Lay Rescuers

1. Evaluate patient for symptoms suggesting heart attack.

2. Call 911 or activate local EMS system.

3. Make patient as comfortable as possible.

Is the patient conscious and able to swallow normally?
No - DO NOT PROCEED WITH ASPIRIN THERAPY
Yes - Ask the patient the following questions:

Do you have a known allergy to aspirin?
Yes - DO NOT PROCEED WITH ASPIRIN THERAPY

Has any physician ever told you not to take aspirin?
Yes - DO NOT PROCEED WITH ASPIRIN THERAPY.

Do you have any stomach ulcer disease or history of vomiting blood?
Yes - DO NOT PROCEED WITH ASPIRIN THERAPY

Do you take any blood thinners such a s coumadin, warfarin or anti-platelet drugs?
Yes - DO NOT PROCEED WITH ASPIRIN THERAPY
If the answer to ALL four questions is NO, the lay rescuer should offer two chewable (162 mg) baby aspirins or up to one five grain (325 mg.) adult aspirin tablet with water.

References:

1. N.E.J.M. 1991; 325:1261-1266.
2. B.M.J. 1994; 308:81-106.
3. McEvoy(Ed), *American Hospital Formulary Service 98 Drug Information*. Bethesda, Maryland: American Society of Health System Pharmacists; 1998.
4. "Anticoagulation and Antiplatelet Therapy in Emergency Medicine: An Evidence Based, State-of-the-Art Review Part I: Aspirin, Glycoprotein Iib/IIIa Inhibitors, and ADP Platelet Receptor Antagonists*"; Emergency Medicine Reports*; 19(24), Nov 23, 1998 p.25
5. Hart RG, Harrison JG. *Stroke* 1996; 4: 585-587.
6. Second International Study of Infarct Survival Collaborative Group(ISIS II), Lancet 1988;2:349-360. and Hennekens, C.H., et. Al, Arch Intern Med 154(1): 37, January 10, 1994.
7. Emergency Medicine News, Vol 21(4), p.1 &20, April, 1999.
8. Jaffy, MB, Meischke H. Eisenberg MS: "Prevalence of aspirin use among patients calling 9-1-1 for chest pain", Academic Emergency Medicine 5:146; p.1149 (1998).
9. GUSTO Group Report: N. Engl J Med. 1993; 329;673-682..
10. ISIS-2 (Second International Study of Infarct Survival, Collaborative Group) Lancet. 1988;2:349-360).
11. ISIS-3; Lancet. 1992;339;753-770).
12. Eric H. Awtry and Joseph Loscalzo "Aspirin"; Circulation, 2000;101:1206-1218.
13. Marciniak TA, Ellerbeck EF, et.al., "Improving the Quality of Care for Medicare Patients with Acute Myocardial Infarction: results from the Cooperative Cardiovascular Project", J.A.M.A. 1998; 279:1315-1317.
14. 14. Stafford, RS; "Aspirin Use Is Low Among United States Outpatients with Coronary Artery Disease"; Circulation, 2000;101:1097-1101.
15. USFDA, New Information for Healthcare Professionals on the Concomitant Use of Ibuprofen and Aspirin, www.fda.gov/cder/drug/InfoSheets, 2006.
16. American Heart Association, Aspirin as a Therapeutic Agent in Cardiovascular Disease, Circulation, 96: 2751-2753, 1997.
17. Rhoden-Jullig, A. M. Britton, K. Malmquist, B. Leijd, Aspirin int the prevention of progressing stroke: a randomized controlled study, J. Internal Med., 254: 584, 2003.
18. Ridker, PM, Cook, NR., Lee, IM., et al., A Randomized Trial of Low Dose Aspirin in the Primary Prevention of Cardiovascular Disease in Women, NEJM., 352: 1293-1303, 2005
19. Patrono, C., LA Garcia Rodriguez, R. Landolfi C., Baigent, Low-Dose Aspirin for the Prevention of Atherothrombosis, NEJM., 353: 2373-2383, 2005.
20. US Food and Drug Administration, Concomitant Use of Ibuprofen and Aspirin: Potential for Attentuation of the Anti-Platelet Effect of Aspirin, Science Paper, 2006.

References Triennial 2012

1. Markenson D, Ferguson JD, Chameides L, et al. Part 17: first aid: 2010 American Heart Association and American Red Cross Guidelines for First Aid. *Circulation.* Nov 2 2010;122(18 Suppl 3):S934-946.

2. Berg RA, Hemphill R, Abella BS, et al. Part 5: adult basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* Nov 2 2010;122(18 Suppl 3):S685-705.

3. Zeymer U, Junger C, Zahn R, et al. Effects of a secondary prevention combination therapy with an aspirin, an ACE inhibitor and a statin on 1-year mortality of patients with

acute myocardial infarction treated with a beta-blocker. Support for a polypill approach. *Curr Med Res Opin.* Aug 2011;27(8):1563-1570.

4. Sai Y, Kusaka A, Imanishi K, et al. A randomized, quadruple crossover single-blind study on immediate action of chewed and unchewed low-dose acetylsalicylic acid tablets in healthy volunteers. *J Pharm Sci.* Sep 2011;100(9):3884-3891.

5. Fuchs I, Spiel AO, Frossard M, Derhaschnig U, Riedmuller E, Jilma B. Platelet hyperfunction is decreased by additional aspirin loading in patients presenting with myocardial infarction on daily aspirin therapy. *Crit Care Med.* Jun 2010;38(6):1423-1429.

6. Fornasini M, Yarzebski J, Chiriboga D, et al. Contemporary trends in evidence-based treatment for acute myocardial infarction. *Am J Med.* Feb 2010;123(2):166-172.

7. Hermanides RS, Ottervanger JP, Dambrink JH, et al. Suboptimal anticoagulation with pre-hospital heparin in ST-elevation myocardial infarction. *Thromb Haemost.* Oct 2011;106(4):636-640.

8. Berwanger O, Guimaraes HP, Laranjeira LN, et al. Effect of a multifaceted intervention on use of evidence-based therapies in patients with acute coronary syndromes in Brazil: the BRIDGE-ACS randomized trial. *JAMA.* May 16 2012;307(19):2041-2049.

9. Morse MA, Todd JW, Stouffer GA. Optimizing the use of thrombolytics in ST-segment elevation myocardial infarction. *Drugs.* Oct 1 2009;69(14):1945-1966.

10. Sigmundsson TS, Gunnarsson B, Benediktsson S, Gunnarsson GT, Duason S, Thorgeirsson G. Management of patients with STEMI transported with air-ambulance to Landspitali University Hospital in Reykjavik. *Laeknabladid.* Mar 2010;96(3):159-165.

11. Bazzino O, et al. Management of acute coronary syndromes in developing countries: acute coronary events-a multinational survey of current management strategies. *Am Heart J.* Nov 2011;162(5):852-859 e822.

12. Hoshida S, Yuasa F, Lim YJ, Kijima Y, Iwasaka J, Iwasaka T. Differences in the mode of presentation for acute coronary syndrome by pre-hospitalization medication, in relation to coronary risk factors, East-Osaka acute coronary syndrome (EACS) registry. *Atherosclerosis.* Nov 2011;219(1):355-360.

13. Chin CT, Roe MT, Fox KA, et al. Study design and rationale of a comparison of prasugrel and clopidogrel in medically managed patients with unstable angina/non-ST-segment elevation myocardial infarction: the TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes (TRILOGY ACS) trial. *Am Heart J.* Jul 2010;160(1):16-22 e11.

14. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet.* Aug 13 1988;2(8607):349-360.

15. Barbash IM, Freimark D, Gottlieb S, et al. Outcome of myocardial infarction in patients treated with aspirin is enhanced by pre-hospital administration. *Cardiology.* 2002;98(3):141-147.

16. Casaccia M, Bertello F, De Bernardi A, Sicuro M, Scacciatella P. [Prehospital management of acute myocardial infarct in an experimental metropolitan system of medical emergencies]. *G Ital Cardiol.* Jun 1996;26(6):657-672.

17. Freimark D, Matetzky S, Leor J, et al. Timing of aspirin administration as a determinant of survival of patients with acute myocardial infarction treated with thrombolysis. *Am J Cardiol.* Feb 15 2002;89(4):381-385.
18. Quan D, LoVecchio F, Clark B, Gallagher JV, 3rd. Prehospital use of aspirin rarely is associated with adverse events. *Prehosp Disaster Med.* Oct-Dec 2004;19(4):362-365.