# Guidelines for Medical Uses of Aspirin

**(October 2014)**


**PAKISTAN ASPIRIN FOUNDATION**

**(Forum for Thrombosis and Atherosclerosis)**

**Website: www.pakaspirin.org.pk**

*Update: October 21, 2014*

# Acknowledgement

Revision and update of Guidelines on Medial Uses of Aspirin has been long overdue. It was about three years ago that Pakistan Aspirin Foundation decided to revise this document. Prof. Abdus Samad an eminent interventional cardiologist, founder member of PAF who has also served as President of Pakistan Aspirin Foundation was entrusted this responsibility as Chairperson of this group which included Prof. Ejaz Ahmad Vohra, another noted physician, former President of PAF, Prof. Muhammad Akbar Chaudhry another former President of Pakistan Aspirin Foundation and Mr. Shaukat Ali Jawaid.

The initial draft was prepared after detailed discussion and meetings between Prof. Abdus Samad and Prof. Ejaz Ahmad Vohra which was then shared with other important members of the Pakistan Aspirin Foundation for their input and feedback. Once their comments and suggestions were received, they were discussed in detail A major contribution to these guidelines was made by Lt. Gen. Mahmood Ahmad Akhtar Former Surgeon Gen. Pakistan Army who is an authority on clinical pharmacology. Pakistan Aspirin Foundation and its members are grateful to him for his contributions.

Others who have contributed include Prof. Khawar Kazmi from Aga Khan University, Dr. Shaukat Malik from Islamabad, Maj. Gen. Ashur Khan another former President of Pakistan Aspirin Foundation. Prof. M. Ishaq, Prof. Feroze Memon from Hyderabad, Prof. Waris Qidwai, Prof. Ijaz Ahmad From Multan, Dr. Bashir Haneef, Prof. Mansoor Ahmad from Karachi, Prof. Nazir Memon, Dr. Fazlur Rehman from Hyderabad, and many others who participated in the discussion during the CME meetings on Medical Uses of Aspirin which we organized at different cities in Pakistan also deserve to be acknowledged. Benefitting from their expertise, their suggestions were incorporated while finalizing these guidelines. We also had the blessings of Dr. Maqbool H. Jafary another former President of Pakistan Aspirin Foundation to compile this document. I did my best to co-ordinate and organize these group meetings.

Once the feed back was received, Prof. Abdus Samad and Prof. Ejaz Ahmad Vohra along with Prof. Muhammad Akbar Chaudhry went through the whole document once again as it required lot of further additions and editing in various sections with the addition of relevant references. This exercise has been going on now for many months before we were able to come up with the final document. The main reason for the revision of these guidelines was the availability of lot of new data based on different studies, ever increasing literature on emerging indications for use of Aspirin besides risk calculation. We gratefully acknowledge that we have benefitted immensely from the Framingham Risk Score Sheet developed by The Heart Institute of Doylestown Hospital which contains Framingham Risk Score calculator for Men and Women separately which the physicians will find extremely informative to calculate the likely risk of the patient before putting them on Aspirin therapy. Every effort has been made to make it a comprehensive document on Medical Uses of Aspirin supported with relevant references.

Pakistan Aspirin Foundation is also extremely grateful to Atco Laboratories which has been sponsoring our Continuing Medical Education programmes for the last many years and it also helped us to get feed back from our colleagues at different meetings which we had organized during the last couple of months while these guidelines were being revised.

Shaukat Ali Jawaid October 21, 2014
General Secretary

# Executive Summary

Aspirin remains the cornerstone of anti platelet therapy in patients with cardiovascular diseases. It decreases mortality and recurrence of cardiovascular events when used as acute therapy following acute coronary syndrome, thrombotic stroke and Kawasaki's disease. It has proven benefits in secondary prevention in acute coronary syndrome, stable angina, revascularization, stroke, TIAs. As such Use of Aspirin in ST elevation Myocardial Infarction or Acute Coronary Syndrome offers a substantial benefit regarding mortality, re-infarction and stroke.

Use of Aspirin in primary prevention is associated with clinical benefit only in high risk individuals. The physicians starting an individual for a life long low dose aspirin therapy for primary prevention must calculate the overall risk of the individual and only high risk patients should be advised to start low dose aspirin Therapy.

Patients with diabetes mellitus should also be put on low dose aspirin therapy if there are no contra-indications.

Patients with high blood pressure may be started on low dose aspirin only when their blood pressure is well controlled for a prolonged period of time.

The role of Aspirin in prevention of deep vein thrombosis in major surgery and Air travel is still under investigation. Another emerging indication is prevention of colorectal cancer and other major cancers including reduction in distant metastasis.

Enteric coated aspirin preparations developed to attenuate local gastric erosion and minimize this side effect are preferred for long term use in patients on low dose aspirin therapy. The concept of aspirin resistance is still an emerging and important clinical question which needs to be studied further

These guidelines also give some details of combination with Clopidogrel in acute coronary syndrome and coronary stenting as well as CABG.

*Prof. Abdus Samad* *Prof. Ejaz Ahmed Vohra* *Prof. M. Akbar Chaudhary* *Shaukat Ali Jawaid*

# Guidelines for Medical Uses of Aspirin

1. Acute myocardial infarction (AMI)
2. Acute Coronary Syndromes (ACS)
3. Secondary prevention of Acute Myocardial Infarction (AMI)
4. Primary prevention Coronary Artery Disease (CAD)
5. Acute Ischemic Strokes
6. Transient Ischemic Attacks (TIAs)
7. Primary and secondary prevention of strokes
8. Hypertension
9. Diabetes Mellitus
10. Acute Rheumatic Fever
11. Prophylaxis against Deep Vein Thrombosis and Pulmonary Embolism (DVT/PE)
12. Emerging Uses
    - Pregnancy
    - Phospholipid Antibody Syndrome
    - Cancer ● Colorectal
        ● Other Cancers

## 1. INTRODUCTION

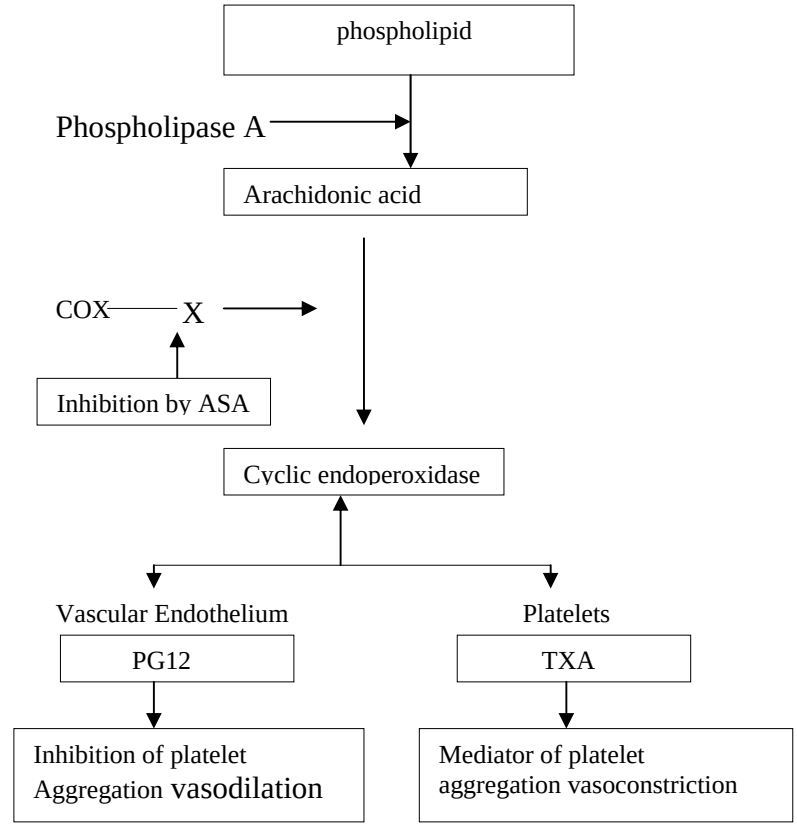
Aspirin and its effect on platelet aggregation has been extensively studied in thromboembolic disease both for prevention and treatment. Antiplatelet trialist collaboration in 1988 showed that ASA significantly reduced the risk of thromboembolic disease by 25 to 30 percent. The totality of evidence from basic research, clinical investigations, observational epidemiological studies, and more than 100 randomized clinical trials in high risk patient has provided strong support for the net benefits of aspirin in decreasing the risk of vascular death by 15% and nonfatal vascular events by 30% in a wide range of patients.

- In secondary prevention of CVD after acute myocardial infarction (MI), occlusive stroke, transient ischemic attack (TIA), stable angina, and coronary artery bypass surgery to reduce risks of MI, stroke and vascular death.
- In acute ischemic syndromes such as acute MI and unstable angina (USA) to reduce riks of recurrent MI, STROKE, AND CARDIOVASCULAR DEATH.
- In Acute Ischemic stroke and recurrent stroke.
- In primary prevention of a first CVD event in individuals at moderate to high risk.
- It has also been used in placental insuffiency, in some cases of atrial fibrillation and prevention of pulmonary embolism.

## 2. MECHANISM OF ACTION

Aspirin permanently inhibit the COX activity of prostaglandin H1 Synthatase (COX1) and prostaglandin H2 Synthatase (COX2). Platelet and vascular endothelium process PGH2 to produce the TXA2 and PG12 respectively. TXA induces platelet aggregation whereas PGI 2 inhibit platelet aggregation. TXA2 is derived from COX1 (platelet and high sensitive aspirin)

There is also transient inhibition of PG12 production. Cox2 mediated PGA2 production occurs and is relatively insensitive to aspirin.




## 3. ASPIRIN PHARMACOKINETICS:

1. Rapidly absorbed from stomach and upper intestine.
2. Plasma level peak after 30-40 minute after ingestion.
3. Antiplatelet effect evident at 1 hour.
4. Enteric coated aspirin takes 3-4 hour for its effects. In emergency situation if enteric coated aspirin is the only available then it should be chewed rather than swallowed.
5. Some enteric coated aspirin have lower bioavailability.

## 4. USE OF ASPIRIN IN ACUTE ST ELEVATION MYOCARDIAL INFARCTION

Acute ST Elevation myocardial infarction is a life threateining catastrophic event & is a result of total occlusion of a major coronary artery due to clot formation as a result of plaque rupture or plaque abrasion. The sudden cessation of myocardial blood flow results in adverse electrical & mechanical dysfunction putting the victim's life in dire danger.

Rapid revascularization utilizing primary angioplasty, clot suction followed by Drug Eluting stent has proven to be the best course of action. Antiplatelet therapy with soluble Aspirin 300 mg should be started immediately on 1st contact with the victim. This dose should be continued for 3 months & thereafter 75-100 mg of Aspirin daily may be given for indefinite period. The starting of Aspirin in this situation reduces mortality by about 23%.

***Recommendations:***

It is recommended that all patients suspected of Acute MI whether displaying ST elevation or ST depression or Bundle Branch Block (BBB) should use one tablet of soluble Aspirin (300mg) immediately followed by (150mg) (half a tablet ) daily orally for 3 months. The concomitant use of ACE Inhibitors with Aspirin in Acute MI is safe & is recommended.

**In acute emergency only soluble Aspirin 300mg should be used.**
*Ref. BNF Sept.2012*

Table-I: Results of 1st 5 weeks of Aspirin therapy in suspected evolving AMI

| End Points | Aspirin 150mg/day (n= 8585) | Placebo 1 tab/day (n=8600) | Results %±SD |
|---|---|---|---|
| Non fatal reinfarction | 83 | 170 | 50 ± 9 |
| Non fatal stroke | 27 | 51 | 46 ± 17 |
| Fatal CV mortality | 804 | 1014 | 23 ± 4 |
| Any vascular event | 914 | 1237 | 23 ± 4 |

Patients undergoing Primary Coronary Angioplasty should also receive 600mg of Clopidogrel or newer Antiplatelet agent as a loading dose & then 75mg per day at least for one year.

***Healthcare professionals are advised to promote the use of inexpensive, economically priced Aspirin which is the ideal antiplatelet therapy. Enteric coated aspirin therapy is preferred because of its safety in long term use.***

Table-II: Effect of anti-platelet therapy on vascular events

| *Category of trial* | *No. of trials with data* | *Anti-platelet, percent** | *Adjusted controls, percent** | *Odds reduction, percent** |
|---|---|---|---|---|
| Prior MI | 12 | 13.5 | 17.0 | 25±4 |
| Acute MI | 15 | 10.4 | 14.2 | 30±4 |
| Prior stroke / TIA | 21 | 17.8 | 21.4 | 22±4 |
| Acute stroke | 7 | 8.2 | 9.1 | 11±3 |
| Other high risk | 140 | 8.0 | 10.2 | 26±3 |
| Unstable angina | 12 | 8.0 | 13.3 | 46±7 |
| Stable angina / CHD | 7 | 9.9 | 14.1 | 33±9 |
| Peripheral arterial disease | 42 | 5.8 | 7.1 | 23±8 |
| All trials (high or low risk) | 195 | 10.7 | 13.2 | 22±2 |
| All low risk Δ (primary prevention) | 3 | 4.5 | 4.9 | 10 |

* Percent of patients suffering vascular events who are treated with antiplatelet agents or placebo; the duratin of treatment was two years with a prior MI or stroke/ITA, 30 days with an acute MI, three week with an acute stroke, and two years for other high-risk patients.
* Odds reduction of vascular events due to antiplatelet therapy.
Δ ***Data from: Antiplatelet Trialist' Collaboration, BMJ 1994; 308:81.***

## 5. Aspirin Use in Secondary Prevention

Low dose Aspirin is of definite and substantial net benefit for patients who are suffering from occlusive coronary artery disease. In a meta analysis (Fig.1) of 16 secondary prevention trials involving 17000 patients (43000 patients years & 33061 vascular events compared long term use of Aspirin with control. Aspirin therapy resulted in an significant risk reduction and a non significant increase in bleeding (Fig.2).

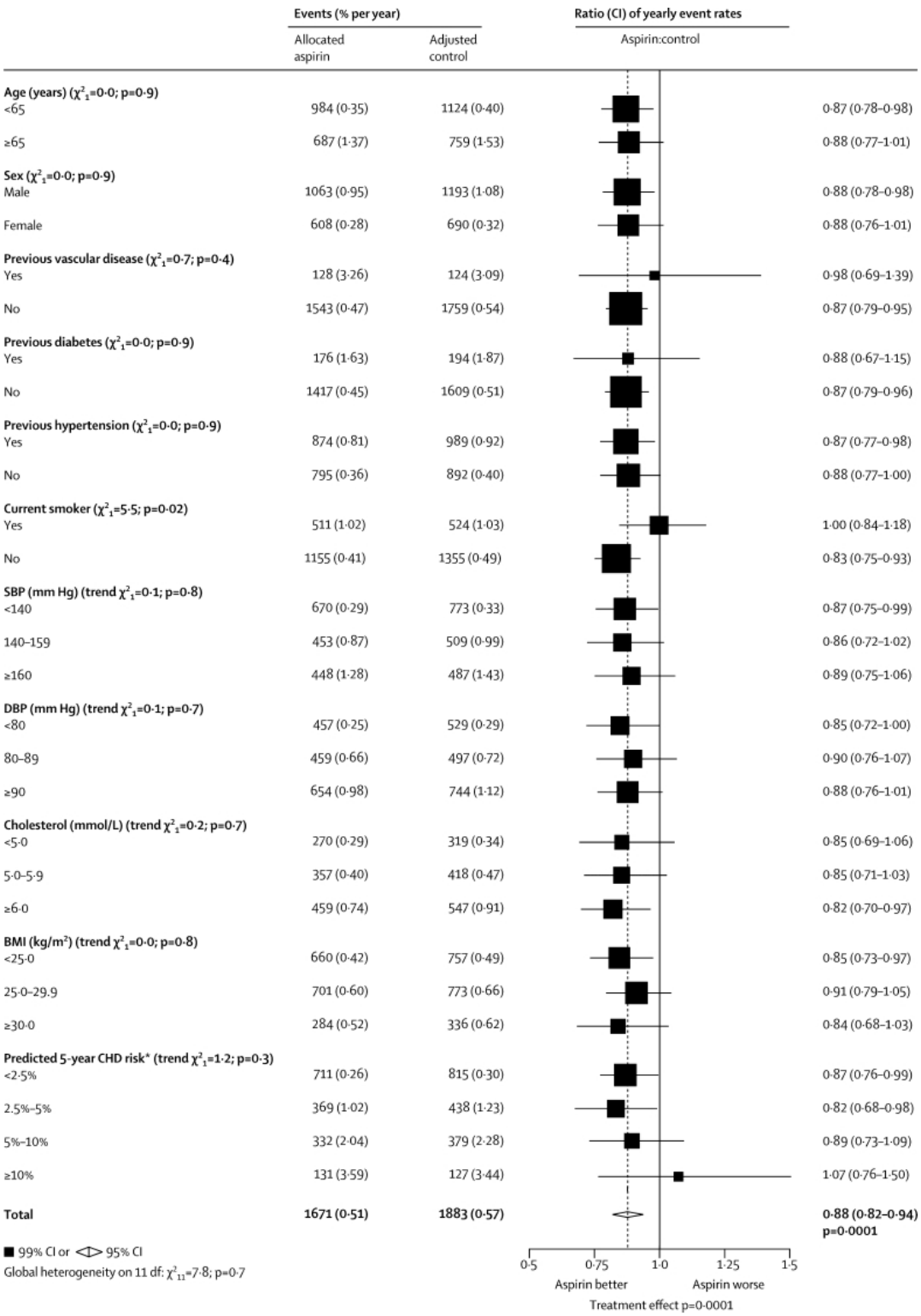



Fig.1: Serious vascular events in primary prevention trials-subgroup analyses. Actual numbers for Aspirin-allocated trial participants, and adjusted numbers for control-allocated trial participants, are presented, together with the corresponding mean yearly events rate (in parentheses). Rate ratio (RRS) for all trials are indicated by squares and their 99% CIs by horizontal lines. Subtotals and their 95% CIs are represented by diamonds. Squares or diamonds to the left of the solid line indicate benefit. A global test for heterogeneity ($X^2$ on 11 degree of freedom) is provided. Unknown values are not plotted. SBP = Systolic Blood Pressure. DBO = Diastolic Blood Pressure. BMI = Body Mass Index. CHD = Coronary Heart Disease. * Excluding patients with a history of vascular disease.

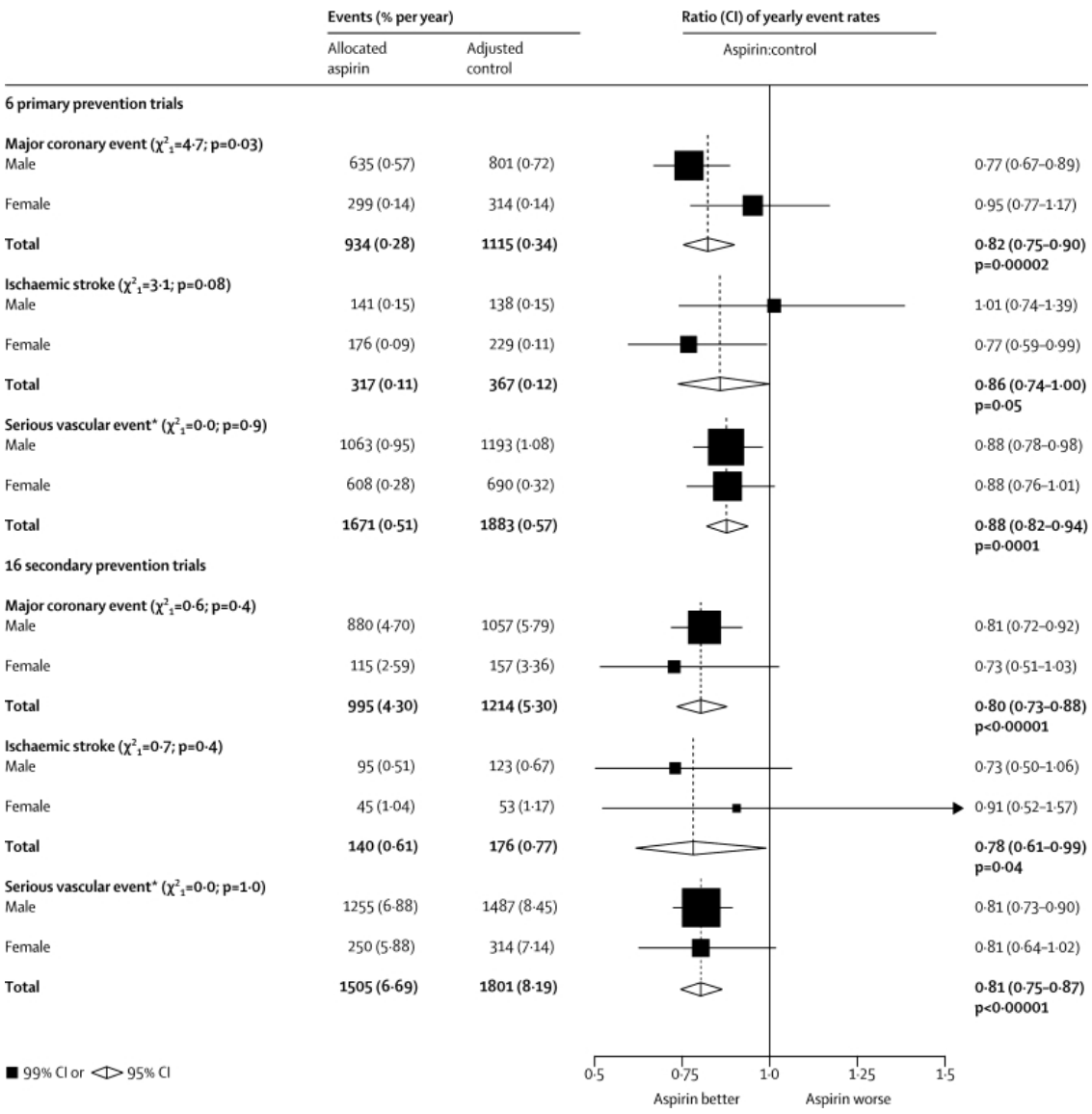



Fig.2: Selected outcomes in primary and secondary prevention trials of aspirin, by sex.
Actual numbers for aspirin-allocated trial participants, and adjusted numbers for control-allocated trial participants, are presented together with the corresponding mean yearly event rate (in parentheses). Rate ration (RRs) for all trials are indicated by square and their 99% CIs by horizontal lines. Subtotals and their 95% CIs are represented by diamonds. Square or diamonds to the left of the solid line indicate benefit. * Myocardial infarction, stroke (haemorrhagic or other), or vascular death.

***Recommendation:***

All patients who have suffered a coronary event in the past or has evidence of coronary artery disease (ETT, Nuclear Scan or Angio) or peripheral vascular disease should receive (75-100 mg) of Aspirin daily for an indefinite period of time up to eighty years of age and then if advised by the physician.

## 6. ASPIRIN IN PRIMARY PREVENTION:

Although preventive steps for primary prevention of coronary artery disease must begin as early in the life of an individual as possible (preferably 3-5 years of age) including life style modification involving discretions regarding the amount & type of diet, physical activity & mental solace and placatory attitudes as well as proper rest and sleep. Avoiding smoking is the corner stone of primary & secondary prevention. The use of long term (even life long) medications (Aspirin & Statins) has been advocated. However the results of recent studies (Table-III) have been interpreted varyingly with the resultant diversity in the opinions as regard primary prevention. All physicians considering Aspirin therapy for primary prevention in an individual must calculate the risk for future events using the Framinghom risk score. Only individuals with high risk may be started with daily aspirin therapy, middle risk individual may be started on therapy if the patients agree to the small benefit vs the side effects of this long term therapy. (G1 bleed, Hemorrhagic stroke)

## 7. ASPIRIN USE IN ACUTE CORONARY SYNDROME

Use of Aspirin is associated with a reduced risk of Acute Myocardial Infarction & death by 50%. The dose of Aspirin in this situation is 300mg for 3 months & to be continued as 75-100mg daily thereafter indefinitely. Patients undergoing primary angioplasty should also receive Clopidogrel 300-600mg as a loading dose and 75mg/day subsequently.

## 8. ASPIRIN AFTER PCI

Aspirin should be administered in a dose of (150mg) daily for one month & then (75-100mg) daily for indefinite periods. Clopidogrel in 75mg daily dose must be given in addition for at least one year in case of Drug Eluting Stent (DES).

***Anti-Platelet Therapy***

Aspirin and many other Anti-Platelet Drugs are now available. Studies have shown that Aspirin use has a vast therapeutic applications. However, at present the major problem is irrational misuse of other anti-platelet drugs i.e. Clopidogrel and Prasugrel. There is a dire need to rationalize the use of these anti-platelet drugs.

Table-III: Design and eligibility criteria of primary prevention aspirin trials

| | Dates of recruitment | Participating countries | Year of main publication | Number of participants | Mean duration of follow-up (years) | Target population | Eligible age range (years) at entry | Aspirin regimen | Randomized factorial comparison | Placebo control |
|---|---|---|---|---|---|---|---|---|---|---|
| British Doctors' Study[23] | November 1978–November 1979 | UK | 1988 | 5139 | 5.6 | Male doctors | 19–90 | 500 mg daily | None | No |
| US Physicians' Health Study[24] | August 1981–April 1984 | USA | 1988 | 22 071 | 5.0 | Male doctors | 45–73 | 325 mg on alternate days | β-carotene vs. placebo | Yes |
| Thrombosis Prevention Trial[17] | February 1989–May 1994 | UK | 1998 | 5085 | 6.7 | Men with risk factors for CHD | 45–69 | 75 mg daily | Warfarin vs. placebo | Yes |
| Hypertension Optimal Treatment Trial[18] | October 1992–May 1994 | Europe, North and South America, Asia | 1998 | 18 790 | 3.8 | Men and women with DBP 100–115 mmHg | 50–80 | 75 mg daily | Three blood pressure regimens | Yes |
| Primary Prevention Project[19] | June 1993–April 1998 | Italy | 2001 | 4495 | 3.7 | Men and women with one or more risk factors for CHD | 45–94 | 100 mg daily | Vitamin E vs. open control | No |
| Women's Health Study[25] | September 1992–May 1995 | USA | 2005 | 39876 | 10.0 | Female health professionals | 45 or older | 100 mg on alternate days | Vitamin E vs. placebo | Yes |
| Prevention of Progression of Arterial Disease and Diabetes Trial[20] | November 1997–July 2001 | UK | 2008 | 1276 | 6.7 | Men and women with type 1 or 2 diabetes and ABI $\leq$0.99 | $\geq$40 | 100 mg daily | Antioxidant vs. placebo | Yes |
| Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Trial[21] | December 2002–May 2005 | Japan | 2008 | 2539 | 4.4 | Men and women with type 2 diabetes | 30–85 | 81 or 100 mg daily | None | No |
| Aspirin for Asymptomatic Atherosclerosis Trial[22] | April 1998–December 2001 | UK | 2010 | 3350 | 8.2 | Men and women with ABI $\leq$0.95 | 50–75 | 100 mg daily | None | Yes |



***Ref:*** Patrono C. Low dose aspirin in primary prevention: cardio protection, chemoprevention, both, or neither? EUR Heart J. 2013;34:3403-3411. Doi: 10.1093/eurheartj/eht058

## 9. Combination Therapy:

***The use of Clopidogrel in combination with Aspirin.***

The combination of clopidogrel with Asprin is recommended for the treatment of "Acute Coronary Syndrome" without ST Segment, Elevation. The initial dose of clopidogrel is 300mg and the maintenance dose in 75mg. The evidence of benefit of asprin and clopidogrel combination is for Three months period. However it may be used for the maximum period of twelve months and after that Aspirin alone is recommended for treatment for an indefinite period for secondary prevention of Ischaemic Heart Disease. *Ref. BNF September 2012. NICE guidelines Scottish Medicines Consortium*.

***Risks and Disadvantages associated with the irrational use of combinations of aspirin and Clopidogrel and aspirin and Prasugrel:*** The inappropriate use of combinations of these drugs and for indefinite periods can cause serious GI Hemorrhages.

***Protection of GI Tract when taking Aspirin plus Clopidogrel therapy:***

Esomeprazole, Pentoprazole or H2 Antagonist like Famotodine should be used and not Meprozole which has HAL Interactions with Clopidogrel.

Low dosage aspirin and Ibuprofen if given together, Ibuprofen may affect anti-platelet activity of aspirin. In order to avoid it there should be sufficient spacing.

***Clopidogrel Side Effects:*** As compared to low dose aspirin, clopidogrel has many serious side effects like suppression of bone-marrow leucopoenia, agranulocytosis, thrombo-cytopoenia: serious hypersensitivity reactions. *Ref. BNF September 2012.*

**Table-IV: Recommendation regarding use of Aspirin for Prevention of MI and Stroke**

| **Population** | **Men** | **Women** | **Men** | **Women** | **Men & Women** |
|---|---|---|---|---|---|
| | **Age 45 -79 Years** | **Age 55 -79 Years** | **< 45 Years** | **<55 Years** | **> 80 Years** |
| **Recommendation** | **Encourage Aspirin use with potential CVD benefit (MIs Prevented) outweighs potential harm of GI hemorrhage** | **Encourage Aspirin use with potential CVD benefit (Stroke Prevented) outweighs potential harm of GI hemorrhage** | **Do not encourage Aspirin use for MI prevention** | **Do not encourage Aspirin use for Stroke prevention** | **No recommendation** |
| | **GRADE A (Strong positive evidence)** | | **GRADE D (Strong Negative evidence)** | | **GRADE 1 (Insufficient evidence)** |

***Reference:*** Annals of Internal Medicine 2009:Vol.150;No.6: March 17, 2009.

## 10. LOW DOSE ASPIRIN & CABG:

Patients on low dose aspirin undergoing CABG surgery may continue taking low dose aspirin while clopidogrel should be stopped one week before the operation. Later Aspirin should be given in a dose 75-150mg daily for indefinite period.

## 11. USE OF ASPIRIN IN ACUTE ISCHAEMIC STROKE

In Acute Ischaemic Stroke Aspirin is the only proven beneficial antiplatelet agent. The International Stroke Trial (IST) and Chinese Acute Stroke Trial (CAST) suggest that Aspirin should be started as soon as possible after the onset of ischaemic stroke; previous trials have already shown that continuation of low dose Aspirin gives protection in the longer term.

***Recommendations:*** It is recommended that patients with acute ischemic stroke be started on 300 mg Aspirin/day as early as possible and to be continued until the decision is made for secondary prevention. The dose for secondary prevention is 75-150 mg daily on long term basis.

***American Academy of Neurology does not recommend dual antiplatelet therapy in management and prevention of acute ischemic stroke.***

## 12. Use of Aspirin in Atrial Fibrillation:

Use of Aspirin is recommended for Prevention of athero-thrombotic and thrombo-embolic events in patients with Atrial Fibrillation and at least one risk factor for a vascular events and for whom Warfarin is unsuitable. Patients taking Warferin should be given Clopidogrel and Aspirin should be stopped.

## 13. USE OF ASPIRIN IN DIABETES MELLITUS

Aspirin is recommended for primary prevention in patients with diabetes with no previous history of vascular disease if his 10 years risk of developing an event is more than 10% and the risk of major bleeding is low. Diabetic men above 50 years of age, women above 60 years of age who also have one or more of the following risk factors are recommended aspirin for primary prevention.

- Smoking
- Dyslipidemia
- HBP (High Blood Pressure)
- Family history of premature CAD
- Albuminuria

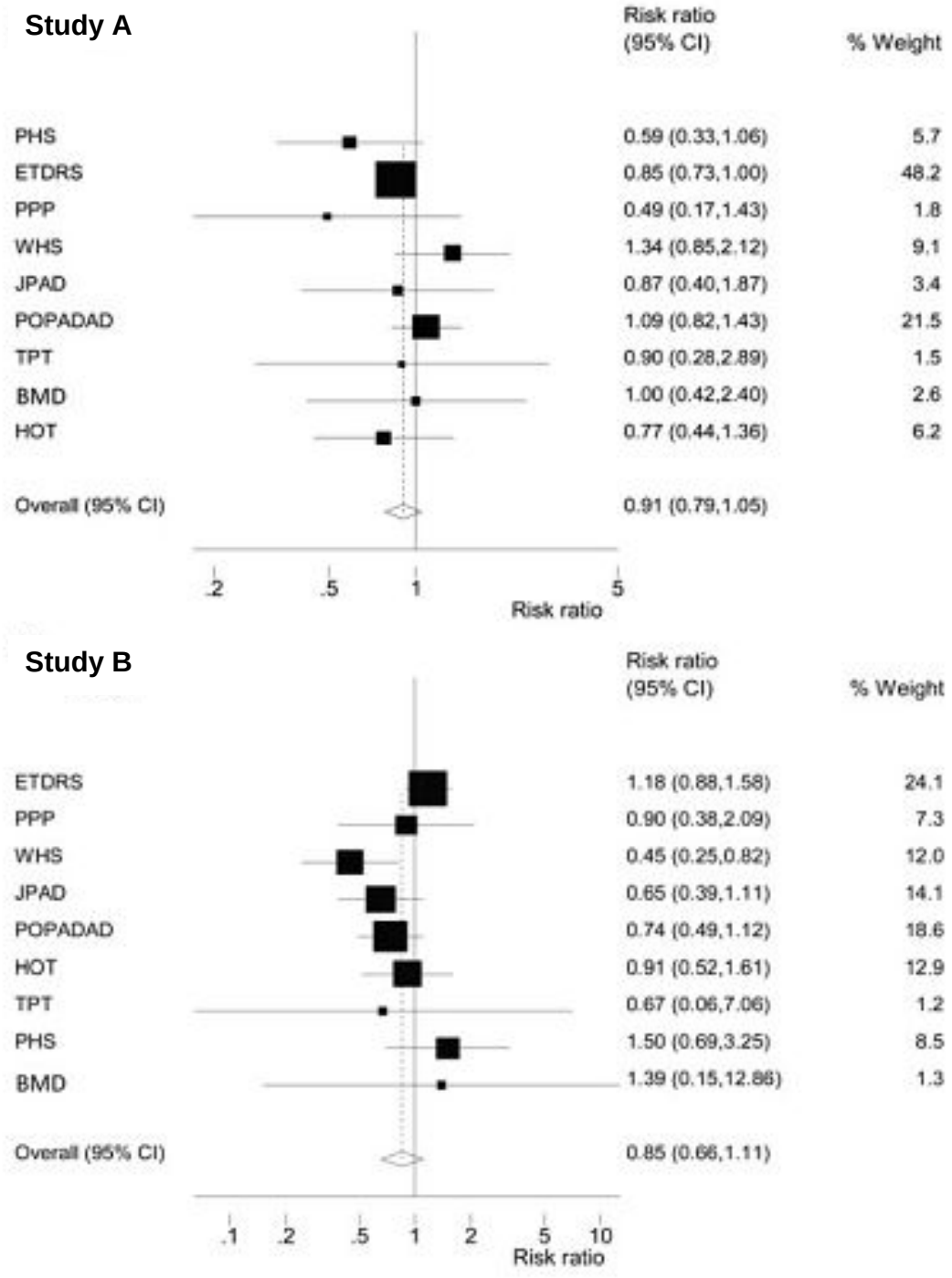



Fig.3: Meta-analysis of trials examining the effects of aspirin on risk of cardiovascular dis-ease events in patients with diabetes. A, Effect of aspirin on coronary heart disease events. Tests for heterogeneity: 2 8.71, P 0.367, I2 8.2%. B, Effect of aspirin on risk of stroke in patients with diabetes. Tests for heterogeneity: 2 12.48, P 0.131, I2 35.9%. BMD indicates British Medical Doctors11 ; CI, confidence inter-val; ETDRS, Early Treatment of Diabetic Reti-nopathy Study18 ; HOT, Hypertension Optimal Treatment14; JPAD, Japanese Primary Preven-tion of Atherosclerosis With Aspirin for Diabe-tes9 ; PHS, Physicians' Health Study12 ; POPADAD, Prevention of Progression of Arte-rial Disease and Diabetes10; PPP, Primary Pre-vention Project15 ; TPT, Thrombosis Prevention Trial13 ; WHS, Women's Health Study. For intermediate risk in DM aspirin may be considered till future research in this group is available. Life long aspirin therapy is not recommended for patients with DM at low risk of CAD (10 years risk less than 5%)

## 14. Risk Calculation:

One of the primary indication for updating these guidelines was to focus on the G1 bleeding risk in person taking long term aspirin therapy. Fair evidence has accumulated on the G1 bleeding & hemorrhagic stroke of this therapy and also use of the great benefit it offers in various preventive usage. Thus physicians must calculate the 10 year risk of all individuals who are candidates for preventive therapies. This is done by calculating the risk by consulting the Framingham Risk Score. (Table-IV-VII)

Convincing evidence exists that Aspirin prevents Myocardial Infarction and stroke. Table-I & II. However there is definite increase in G1 bleeding and also in hemorrhagic stroke in the individuals who take aspirin for prolonged period of time. Thus individuals with net benefit should be advised to take aspirin. However in those whose risk & benefit is balanced, informed consent may be taken if aspirin therapy is started.

Table-V

## FRAMINGHAM RISK SCORING SHEET

Adding Up the Points

| | |
|---|---|
| Age | _____ |
| Total Cholesterol | _____ |
| Smoker | _____ |
| HDL Cholesterol | _____ |
| Blood Pressure | _____ |
| TOTAL | _____ |

About the Framingham Risk Score

In the U.S., many doctors assess a person's risk of heart disease using a risk calculator based on the findings from a large, long-term study conducted in Framingham, Mass. This is referred to as your Framingham risk score. The score uses a system that includes age, sex, total and HDL (good) cholesterol, smoking and blood pressure to assess your 10 year risk of developing heart disease or having a heart attack.

- **Low risk = less than 10% chance**
- **Intermediate risk = 10%-20% chance**
- **High risk = more than 20% chance**

The HEART INSTITUTE of Doylestown Hospital

Table-VI

## FRAMINGHAM RISK SCORE CALCULATOR FOR WOMEN

Your Framingham risk score is your risk of having a heart attack or dying from heart disease within 10 years.

The calculator is NOT intended for men and women who have already had a heart attack or been diagnosed with heart disease. In addition, if you have any of the following conditions, the risk score does not apply to your because you are automatically considered at high risk for heart disease.

- Stroke or mini-stroke (TIA)
- Bypass surgery or balloon angioplasty
- Type 2 diabetes
- Kidney disease
- Abdominal aortic aneurysm (a bulging in the large artery in the stomach wall.)
- A genetic predisposition to very high cholesterol (familial hypercholesterolemia)
- Peripheral artery disease (usually in legs)
- Carotid artery disease (fatty plaque in neck arteries.)

**Estimate of 10-Year Risk for Women (Framingham Point Scores)**

| Age, y | Points |
|---|---|
| 20-34 | -7 |
| 35-39 | -3 |
| 40-44 | 0 |
| 45-49 | 3 |
| 50-54 | 6 |
| 55-59 | 8 |
| 60-64 | 10 |
| 65-69 | 12 |
| 70-74 | 14 |
| 75-79 | 16 |

| Total Cholesterol mg/dL | Points Age 20-39 y | Age 40-49 y | Age 50-59 y | Age 60-69 y | Age 70-79 y |
|---|---|---|---|---|---|
| <160 | 0 | 0 | 0 | 0 | 0 |
| 160-199 | 4 | 3 | 2 | 1 | 1 |
| 200-239 | 8 | 6 | 4 | 2 | 1 |
| 240-279 | 11 | 8 | 5 | 3 | 2 |
| ×280 | 13 | 10 | 7 | 4 | 2 |

| | Points Age 20-39 y | Age 40-49 y | Age 50-59 y | Age 60-69 y | Age 70-79 y |
|---|---|---|---|---|---|
| Non-smoker | 0 | 0 | 0 | 0 | 0 |
| Smoker | 9 | 7 | 4 | 2 | 1 |

| HDL, mg/dL | Points |
|---|---|
| ×60 | -1 |
| 50-59 | 0 |
| 40-49 | 1 |
| <40 | 2 |

| Systolic BP, mm Hg | If Untreated | If Treated |
|---|---|---|
| <120 | 0 | 0 |
| 120-129 | 1 | 3 |
| 130-139 | 2 | 4 |
| 140-159 | 3 | 5 |
| ×160 | 4 | 6 |

| Point Total | 10-Year Risk, % |
|---|---|
| <9 | <1 |
| 9 | 1 |
| 10 | 1 |
| 11 | 1 |
| 12 | 1 |
| 13 | 2 |
| 14 | 2 |
| 15 | 3 |
| 16 | 4 |
| 17 | 5 |
| 18 | 6 |
| 19 | 8 |
| 20 | 11 |
| 21 | 14 |
| 22 | 17 |
| 23 | 22 |
| 24 | 27 |
| ×25 | ×30 |

Table-VII

## FRAMINGHAM RISK SCORE CALCULATOR FOR MEN

Your Framingham risk score is your risk of having a heart attack or dying from heart disease within 10 years.

The calculator is NOT intended for men and women who have already had a heart attack or been diagnosed with heart disease. In addition, if you have any of the following conditions, the risk score does not apply to your because you are automatically considered at high risk for heart disease.

- Stroke or mini-stroke (TIA)
- Bypass surgery or balloon angioplasty
- Type 2 diabetes
- Kidney disease
- Abdominal aortic aneurysm (a bulging in the large artery in the stomach wall.)
- A genetic predisposition to very high cholesterol (familial hypercholesterolemia)
- Peripheral artery disease (usually in legs)
- Carotid artery disease (fatty plaque in neck arteries.)

**Estimate of 10-Year Risk for Men (Framingham Point Scores)**

| Age, y | Points |
|---|---|
| 20-34 | -9 |
| 35-39 | -4 |
| 40-44 | 0 |
| 45-49 | 3 |
| 50-54 | 6 |
| 55-59 | 8 |
| 60-64 | 10 |
| 65-69 | 11 |
| 70-74 | 12 |
| 75-79 | 13 |

| Total Cholesterol mg/dL | Points | | | | |
|---|---|---|---|---|---|
| | Age 20-39 y | Age 40-49 y | Age 50-59 y | Age 60-69 y | Age 70-79 y |
| <160 | 0 | 0 | 0 | 0 | 0 |
| 160-199 | 4 | 3 | 2 | 1 | 0 |
| 200-239 | 7 | 5 | 3 | 1 | 0 |
| 240-279 | 9 | 6 | 4 | 2 | 1 |
| ×280 | 11 | 8 | 5 | 3 | 1 |

| | Points | | | | |
|---|---|---|---|---|---|
| | Age 20-39 y | Age 40-49 y | Age 50-59 y | Age 60-69 y | Age 70-79 y |
| Non-smoker | 0 | 0 | 0 | 0 | 0 |
| Smoker | 8 | 5 | 3 | 1 | 1 |

| HDL, mg/dL | Points |
|---|---|
| ×60 | -1 |
| 50-59 | 0 |
| 40-49 | 1 |
| <40 | 2 |

| Systolic BP, mm Hg | If Untreated | If Treated |
|---|---|---|
| <120 | 0 | 0 |
| 120-129 | 0 | 1 |
| 130-139 | 1 | 2 |
| 140-159 | 1 | 2 |
| ×160 | 2 | 3 |

| Point Total | 10-Year Risk, % |
|---|---|
| <0 | <1 |
| 0 | 1 |
| 1 | 1 |
| 2 | 1 |
| 3 | 1 |
| 4 | 1 |
| 5 | 2 |
| 6 | 2 |
| 7 | 3 |
| 8 | 4 |
| 9 | 5 |
| 10 | 6 |
| 11 | 8 |
| 12 | 10 |
| 13 | 12 |
| 14 | 16 |
| 15 | 20 |
| 16 | 25 |
| ×17 | ×30 |

Table-VIII

# FRAMINGHAM RISK SCORE to predict 10 year ABSOLUTE RISK of CHD EVENT

ST ALBANS & HEMEL HEMPSTEAD NHS TRUST : CARDIOLOGY DEPARTMENT

This risk assessment only applies to assessment for **PRIMARY PREVENTION of CHD**, in people who do not have evidence of established vascular disease.
Patients who *already* have evidence of vascular disease usually have a >20% risk of further events of over 10 years, and require vigorous **SECONDARY PREVENTION**.
People with a Family History of premature vascular disease are at higher risk than predicted; Southern Europeans and some Asians may have a lower risk in relation to standard risk factors.

**STEP 1: Add scores by sex for Age, Total Cholesterol, HDL-Cholesterol, BP, Diabetes and Smoking.** (If HDL unknown, assume 1.1 in Males, 1.4 in Females)

| Age | M | F |
|---|---|---|
| 30-34 | - 1 | - 9 |
| 35-39 | 0 | - 4 |
| 40-44 | 1 | 0 |
| 45-49 | 2 | 3 |
| 50-54 | 3 | 6 |
| 55-59 | 4 | 7 |
| 60-64 | 5 | 8 |
| 65-69 | 6 | 8 |
| 70-74 | 7 | 8 |

| Total Cholesterol | M | F |
|---|---|---|
| < 4.1 | - 3 | - 2 |
| 4.1 – 5.1 | 0 | 0 |
| 5.2 – 6.2 | 1 | 1 |
| 6.3 – 7.1 | 2 | 1 |
| 7.2 | 3 | 3 |

| HDL Cholesterol | M | F |
|---|---|---|
| < 0.9 | 2 | 5 |
| 0.9 - 1.16 | 1 | 2 |
| 1.17 - 1.29 | 0 | 1 |
| 1.30 - 1.55 | 0 | 0 |
| ≥1.56 | - 2 | - 3 |

| Systolic BP | Diastolic BP | | | | |
|---|---|---|---|---|---|
| Male | <80 | 80-84 | 85-89 | 90-99 | ≥100 |
| <120 | 0 | 0 | 1 | 2 | 3 |
| 120-129 | 0 | 0 | 1 | 2 | 3 |
| 130-139 | 1 | 1 | 1 | 2 | 3 |
| 140-159 | 2 | 2 | 2 | 2 | 3 |
| ≥160 | 3 | 3 | 3 | 3 | 3 |
| Female | <80 | 80-84 | 85-89 | 90-99 | ≥100 |
| <120 | - 3 | 0 | 0 | 2 | 3 |
| 120-129 | 0 | 0 | 0 | 2 | 3 |
| 130-139 | 0 | 0 | 0 | 2 | 3 |
| 140-159 | 2 | 2 | 2 | 2 | 3 |
| ≥160 | 3 | 3 | 3 | 3 | 3 |

If Systolic and Diastolic BP fall into different categories, use score from higher category

| Diabetes | M | F |
|---|---|---|
| No | 0 | 0 |
| Yes | 2 | 4 |

| Smoking | M | F |
|---|---|---|
| No | 0 | 0 |
| Yes | 2 | 2 |

| Categorisation of 10 year Risk of CHD Event | |
|---|---|
| Very Low risk | < 10% |
| Low risk | < 15% |
| Moderate risk | 15-20% |
| High risk | > 20% |

**STEP 2: Use total score to determine Predicted 10 year Absolute Risk of CHD Event (Coronary Death, Myocardial Infarction, Angina) by sex**

| Total Score | ≤-2 | -1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 3 | 14 | 15 | 16 | ≥17 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 year Risk: Male | | <2% | 3% | 3% | 4% | 5% | 7% | 8% | 10% | 13% | 16% | 20% | 25% | 31% | 37% | 45% | 53% | 53% | 53% | 53% |
| 10 year Risk: Female | <1% | 2% | 2% | 2% | 3% | 3% | 4% | 4% | 5% | 6% | 7% | 8% | 10% | 11% | 13% | 15% | 18% | 20% | 24% | 27% |

**STEP 3: Compare Predicted 10 year Absolute Risk with "Average" and "Ideal" 10 year Risks, to give Relative Risks**

| Age | 30 - 34 | 35 - 39 | 40 - 44 | 45 - 49 | 50 - 54 | 55 - 59 | 60 - 64 | 65 - 69 | 70 - 74 |
|---|---|---|---|---|---|---|---|---|---|
| "Average" Male | 3% | 5% | 7% | 11% | 14% | 16% | 21% | 25% | 30% |
| "Ideal" Male | 2% | 3% | 4% | 4% | 6% | 7% | 9% | 11% | 14% |
| "Average" Female | < 1% | < 1% | 2% | 5% | 8% | 12% | 12% | 13% | 14% |
| "Ideal" Female | < 1% | 1% | 2% | 3% | 5% | 7% | 8% | 8% | 8% |

| "Ideal" risk represents |
|---|
| Total Cholesterol = 4.1 - 5.1 |
| HDL = 1.2 (Male), 1.4 (Female) |
| BP < 120/80 |
| No Diabetes, Non Smoker |

People with an absolute risk of ≥20% should be considered for treatment: with a Statin to achieve a Total Cholesterol <5 and/or LDL cholesterol <3.2
with anti-hypertensives to achieve a BP ≤160/90 (ideally ≤140/80)

from Wilson PWF, et al Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-47

Dr John Bayliss

## 15. USE OF ASPIRIN IN TRANSIENT ISCHAEMIC ATTACK (TIAs)

The United Kingdom Transient Ischaemic Attack (UK-TIA) Aspirin trial revealed a significant (18%) reduction in the combined rate of non-fatal stroke, non-fatal MI and death when treated with Aspirin.

***Recommendations*** It is recommended that patients with TIA should receive Aspirin 300 mg/day. Dipyridimole or Ticlopidine or Clopidogril may be added in high risk patients.

## 16. PRIMARY AND SECONDARY PREVENTION OF STROKE

Aspirin has been shown to reduce the relative risk of secondary stroke, TIA and death by 25 -31%, while the evidence for primary prevention is still emerging.

***Recommendation:*** The recommended dose for secondary prevention is 75 - 150 mg daily on long-term basis.

## 17. USE OF ASPIRIN IN HYPERTENSION

Hypertension Optimal Treatment (HOT) study has shown definite effectiveness and safety of Aspirin in preventing Acute MI and Stroke in patients with hypertension. (Table -IX).

| **Table-IX: Results of HOT Study** | | **Reduced by** |
|---|---|---|
| **Major cardiovascular events**<br>Acetylsalicylic acid<br>Placebo | <br>315<br>366 | 15% |
| **Major cardiovascular events,**<br>**including silent myocardial infarction**<br>Acetylsalicylic acid<br>Placebo | <br>388<br>425 | 9% |
| **All myocardial infarction**<br>Acetylsalicylic acid<br>Placebo | 82<br>127 | 36% |
| **All myocardial infarction**<br>**including silent cases**<br>Acetylsalicylic acid<br>Placebo | 157<br>184 | 15% |
| **All stroke**<br>Acetylsalicylic acid<br>Placebo | 146<br>148 | 2% |
| **Cardiovascular mortality**<br>Acetylsalicylic acid<br>Placebo | 133<br>140 | 5% |
| Total mortality<br>Acetylsalicylic acid<br>Placebo | 284<br>305 | 7% |

***Recommendations:***

In addition to other measures to control Blood Pressure, 75-100 mg of Aspirin daily should be given to all patients with hypertension on long-term basis. **However in uncontrolled hypertensive patients, Aspirin should be avoided till adequate control of blood pressure is achieved.**

## 18. PROPHYLAXIS AGAINST DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM (DVT/PE)

The results of Pulmonary Embolism Prevention (PEP) trial have shown that patients undergoing hip replacement and other major surgery, Aspirin Therapy produced 43% reduction in Pulmonary Embolism and 36% in symptomatic Deep Vein Thrombosis. The Fatal Pulmonary Embolism was reduced by 58%. There is still uncertainty regarding use of Aspirin for prevention of VTE in high risk patients undergoing surgery.

***Recommendations:*** Aspirin 150mg daily for 6 weeks in PEP trial did showed its efficacy but other agents have superseded its role. Still it has advantage of low cost and safety for use as preventive agent at population level.

## 19. EMERGING USES

**Use of Aspirin in Pregnancy**
**Low dose Aspirin in Pregnancy Induced Hypertension (PIH)**

Low Dose Aspirin may prevent the onset of pre-eclampsia in 15% but has no effect on established pre-eclampsia. Its role in PIH is being investigated. The drug is contraindicated after 36 weeks of pregnancy.

***Cancer:*** Colorectal

The evidence to-date supports that Aspirin reduces the risk of cancer in general and colorectal cancer in particular. A study in 90,000 females nurses revealed 30% reduction in colorectal cancer among those who used Aspirin regularly for 10-19 years and 44% reduction after 20 years consistent Aspirin use. Patients taking Aspirin for the risk of cardiovascular disease may also be reducing their risk of cancer specially colorectal cancer.

***Other Cancers***

There is emerging evidence that low dose aspirin has a role to play in reducing the risk of gastric, oesophageal, prostate and breast cancers and distance metastasis. However, more data is needed for the consensus to develop.

***Dental Treatment:*** Patients getting dental treatment on Low dose Aspirin should not stop aspirin but can reduce the dosage:

*Ref. BNF dental prescribing sept 2012 page 29.*

***Low dose aspirin and Gout:*** Patients suffering from Gout taking zyloric may continue taking low dose aspirin.

***Other Conditions***

Initial indications point to the beneficial effects of Aspirin in prevention of Cataract and Alzheimer's disease.

## 20. CONTRA-INDICATIONS TO ASPIRIN THERAPY

As a general principle all drugs are to be avoided during the 1st trimester of pregnancy.

**Absolute Contra-indications**

Aspirin should not be used in the following conditions:

1. Hypersensitivity to Aspirin and/or other salicylates
2. Haemorrhagic diathesis.
3. Documented acute gastric or duodenal ulcer.
4. Pregnancy after 36 weeks of gestation

**Relative Contra-Indications**

Aspirin is to be used with caution in the following conditions:

i. G6PD deficiency
ii. Breast feeding
iii. Chronic or recurrent peptic ulcer
iv. Bronchial Asthma
v. Severe renal or hepatic damage
vi. Bronchial asthma is one of the contra-indications due to Aspirin sensitivity

21. The causative role of Aspirin in Rye's syndrome in children has been questioned.

| **"Drug - Drug Interaction of Aspirin"** | | | |
|---|---|---|---|
| Many adverse drug events occur as result of drug -drug , drug disease or drug - food interactions and , therefore, are preventable. Clinicians' awareness of the agents that commonly cause drug - induced disorders and its recognition can decrease the likelihood that an adverse event will occur. | | | |
| *Drug* | *Effect* | *Mechanism* | *Management* |
| Acetazolamide (Diamox) | Acidosis due to decrease in elimination of acetazolamide | Increased acetazolamide concentration & shift of salicylates from plasma into tissue | Monitor for salicylate toxicity |
| Alendronate (Fosamax) | GIT adverse effects | Unknown | Aspirin doses may need to be reduced |
| Antacids | Renal elimination of salicylates increases | Decreased absorption (increased urinary pH) | Monitor for reduced effectiveness upon initiation of antacid |
| Cortisone | GIT ulceration | Additive adverse effects | Monitor patients for excessive gastrointestinal side effects GI distress, GI bleeding ,gastric ulceration ) and for decreased effectiveness of aspirin. |
| Diltiazem (Herbessr) | Diltiazem may also cause an increase in bleeding time | Inhibition of ADP induced aggregation | Monitor patients for signs or symptoms of abnormal bleeding |
| Frusemide (Lasix) | Salicylate toxicity at lower aspirin doses than expected | Inhibition of proximal tubular secretion | Avoid doses of greater than 650-mg daily of aspirin when given concurrently with Frusemide. |
| Ketorolac (Toradol) | Risks of inducing NASAIDs related adverse events | Reduced ketorolac plasma protein binding | Concomitant use of ketorolac and aspirin is contraindicated |
| Methotraxate | Methotrexate toxicity | Decreased methotrexate clearance | Monitor closely for toxicity, especially myelosuppression and gastrointestinal toxicity. |
| Spironalactone (Aldactone) | Decrease in the effectiveness of spironolactone | Altered rennin effect | Avoid aspirin doses of greater than 650- mg daily in adults receiving spironolactone |
| Warfarin (Marevan) | If warfarin and aspirin are used concurrently, the dosage should be individualized. | Displacment of warfarain from plasma albumin | Monitor the prothrombin time or international normalized ratio (INR) |

*Reference:* Micromedex computerized drug information 2001

***Note:*** Interaction of Asprin with Methotrexate, Actazalamide, Alendronate, Frusemide etc occur when used in full doses for treatment of inflammatory joint disorders like Rheumatoid etc., when used in low dose it has no interaction of therapeutic significance therefore it is administered with these drugs.

## 22. GASTROINTESTINAL COMPLICATIONS AND ASPIRIN

The most important and frequent side effects of Aspirin are those involving the GIT resulting from the irritation of GI mucosa producing clinical manifestations of various categories.

These may be simple heartburn, nausea, epigastric pain, or GI bleeding of varying intensity. GI bleeding may range from microscopic blood loss to overt gastrointestinal bleeding requiring blood transfusions.

The mechanism of mucosal irritation by Aspirin is controversial and opinions differ as to the exact mode of its production. However, the following facts have been well documented:

1. Gastrointestinal mucosal irritation or production of mucosal lesions of various severity are by and large highly dependant on the dosage and duration of Aspirin administration.
2. Smaller doses especially less than 300 mg/day are associated with a markedly lesser gastrointestinal irritation than larger doses, especially if buccal route or protective coating is used.
3. The principal mechanism is due to the inhibition of COX-1-dependent prostaglandin E2 (PGE2) synthesis by Aspirin, while PGE2 inhibits acid secretion in gastric mucosa and increases mucous formation.

## 23. SAFETY PROFILE OF ASPIRIN

Optimal dosage of Aspirin is yet to be evaluated. However doses of 75-300 mg used in different trials appear to be similarly effective. In this range the risk of side-effect (gastric mucosal injury causing gastrointestinal haemorrhage) is reduced to placebo level. In addition there is no proven benefit of combining it with other antiplatelet agents except in a few specific conditions.

For long term use of Aspirin smaller doses of 75-150mg are recommended. If symptoms of gastric irritation occur, physicians should be consulted before any decision is taken by the patient himself to discontinue the medication.

As shown in Table-X, Aspirin as compared to the Non-Steroidal Anti-inflammatory Drugs has a much better safety profile.

The data supporting that one NSAID is safer than another or safer than Aspirin as regards gastric mucosal injury is equivocal.

***Alcohol Warning:***

If a patient takes three or more alcohol drinks per day, he should contact his physician for advice as to when and how he should take pain relievers including Aspirin.

| **Table-X: Side effects of Aspirin especially compared with NSAIDs as regards bleeding** | |
|---|---|
| NSAIDs Toxicity Index Scores (Fries. et al, 1991) | |
| *Drug* | *Standardized Toxicity index Score* |
| Aspirin | 1.19 |
| Salicylate | 1.28 |
| Ibuprofen | 1.94 |
| Naproxen | 2.17 |
| Sulindac | 2.24 |
| Piroxicam | 2.52 |
| Diclofenac Sodium | 2.6 |
| Fenoprofen | 2.95 |
| Ketoprofen | 3.45 |
| Meclofenamate | 3.86 |
| Tolmetin | 3.96 |
| Indomethacin | 3.99 |

**Note:** Major use of Aspirin is as an anti-platelet agent. It is no more used to treat inflammatory joint diseases. One of the side effects of Aspirin therapy is the likely chances of bleeding. This Toxicity Index Scores has been added to dispel the impression of any increased GI bleeding with Aspirin. As shown in the above table the Toxicity Index Score of Aspirin is much less as compared to NSAIDs which are extensively used.

## 24. PREVENTION AND HEALTH PROMOTION

It should be given utmost importance as the treatment of athero-thrombotic disease is extremely expensive and not very satisfactory.

Prevention of diseases and promotion of health should start before conception and continue throughout life. It has been noted that low-birth weight babies suffer far more from athero-thrombotic diseases therefore female children should be well fed and there should be good anti-natal care Autopsies done on teenage soldiers during the Korean War showed that the seeds of atherosclerosis are laid in childhood. There should be special emphasis on diet as Socrates said “Diet is health and Diet is Medicine” He also said Nutrition ends in Medicine and Medicine ends in Nutrition. Diet should be high in Vegetables, reasonable quantities of fruits, whole grains, low fat dairy products, mono-saturated and poly-unsaturated fats, enough of oily fishes, poultry, nuts and seeds and very low in saturated fat, salt, red meat and be free from transfatty acids. Enough exercise both aerobic and muscle strengthening, and necessary ideal weight should be kept but the important point is to keep abdominal girth in males less than 35 ½”and in females less than 31 ½”.

In South Asians it has been found that the abdominal obesity is the main cause of developing insulin resistance leading of glucose intolerance metabolic syndrome, diabetes mellitus, hypertension, dyslipidaemias and athero-thrombosis diseases. Avoidance of the use of tobacco, stress management and having good sleep according the natural circadian Rhythm are import factors. This is the basis of modern life style therapy. Early screening for risk factors and their early management are helpful in prevention of disorders and promotion of health.

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