

# Thromboprophylaxis with antiplatelet agents in patients with mechanical aortic valves



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# Thromboprophylaxis with antiplatelet agents



## The role of platelets in the high pressure circulation

### A. Characteristics:

1. Rapid flow velocity
2. Turbulent flow
3. High shear stress

These factors cause:

- a. platelet activation and aggregation
- b. Fragmentation of RBC with release of ADP

ADP – causes further platelet activation

# Thromboprophylaxis with antiplatelet agents



Aortic Mechanical Prostheses cause significant downstream turbulence (High Pressure Circulation)

- a) Lead to increased and mixed shear forces downstream.
- b) Cause platelet activation and aggregation.
- c) Fragmentation of RBC with release of ADP that causes further platelet activation.

# Thromboprophylaxis with antiplatelet agents



## Shear Forces: Effect on Platelets

1. Using radiolabelled platelets one can study the adherence of platelets to the components of a prosthesis
2. Platelet activation increases collision frequency among platelets and the surface of the prosthesis.
3. Thrombus formation is preceded by platelet activation.

# Thromboprophylaxis with antiplatelet agents



**Aortic Prostheses** – region of acceleration and high shear stress.

- a. High shear stress: Platelet Activation + Aggregation
- b. RBC damaged      →      ADP released.

❖ *Platelets are activated by this process. The contribution of coagulation factors to thrombotic potential is a secondary phenomenon.*

**Mitral Prostheses** – frequently associated with left atrial enlargement – have slow flow. This produces stasis and prolonged contact of coagulation factors with the damaged endocardial or prosthetic surface.

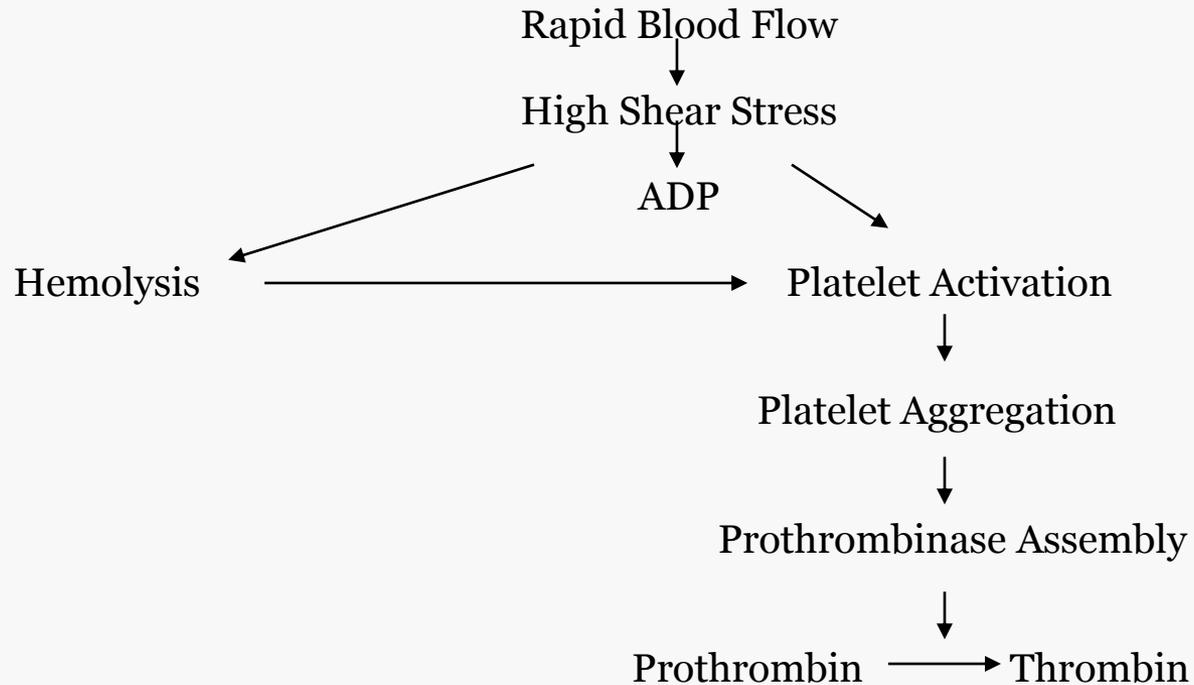
❖ *Platelets are contributory but secondary.*

Becker R.C., Eisenberg P., Turpie AGG. Pathobiologic features and Prevention of thrombotic complications associated with Prosthetic Valves: Fundamental principles and the contribution of platelet and thrombin. Am Heart J 2001; 141:1025-37.

# Thromboprophylaxis with antiplatelet agents



## Thrombogenic Mechanism for Aortic Prostheses

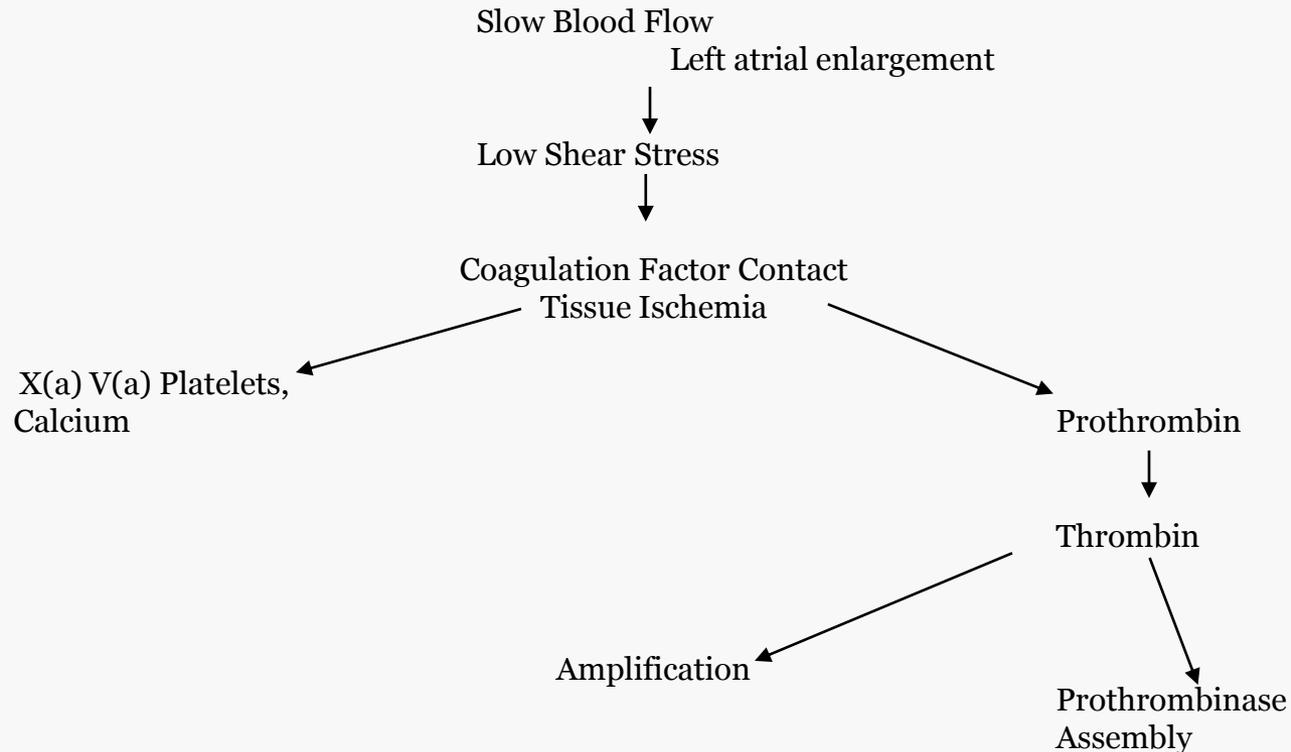


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# Thromboprophylaxis with antiplatelet agents



## Thrombogenic Mechanism for Mitral Prostheses



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# Thromboprophylaxis with antiplatelet agents



1. Platelet mediated events such as acute coronary syndromes and coronary artery stents are treated by inhibiting platelet reactivity with antiplatelet agents.
2. Events in the low pressure circulation (↓velocity, low shear stress and stasis are treated with vitamin k antagonists (warfarin).

## **Treatment of a platelet mediated problem with warfarin: Long term results of a large series of patients with St. Jude aortic mechanical valves treated with warfarin.**

**# patients**  
**2982**

**bleeding complication**  
**589 (2.7%/pt-yr)**

**TE complications**  
**421 (1.9%/pt-yr)**

Emery RW, Krough CC, Aron KV, Emery AM, et al. The St. Jude medical cardiac valve prosthesis: A 25 years experience with single valve replacement. Ann Thorac Surg 2005;79:776-83.

# Thromboprophylaxis with antiplatelet agents



**Aspirin** – irreversibly acetylates platelet cyclooxygenase-1 (Cox-1) and prevents the synthesis of thromboxane A<sub>2</sub> (Tx A<sub>2</sub>) (agonist of platelet aggregation).

## **Clpidogrel**

1. ADP receptor antagonist that irreversibly inhibits the binding of ADP to the P<sub>2</sub>Y<sub>12</sub> receptor on the platelets.
2. ADP is needed for the activation of the GPIIb/IIIa receptor.
3. These receptors bind fibrinogen and hence the formation of fibrin clots. The GPIIb/IIIa receptor blocked by the active metabolite of clopidogrel.

**Prasugrel:** ADP receptor antagonist (binds to P<sub>2</sub>Y<sub>12</sub> receptor)

Clopidogrel and aspirin are successfully used in patients with acute coronary syndromes and patients with coronary stents that are: **platelet mediated events.**

Prasugrel and aspirin: results superior to clopidogrel and aspirin in patients with acute coronary syndromes when managed with PCI. Prasugrel has better absorption than clopidogrel and achieves inhibition of platelet reactivity within one hour.

Van Gestel M.A. Heemskerk, J.W.M. Slaaf, D.W. In vitro blockade of Platelet ADP receptor P<sub>2</sub>Y<sub>12</sub> Reduces Embolus and Thrombus formation but not thrombus stability. *Thromb Vasc Biol.* 2003; 23:518-23.

Van Giezen J.J., Humphries R.G., Preclinical and clinical studies with selective reversible direct P<sub>2</sub>Y<sub>12</sub> antagonists. *Semin thromb Hemost* 2005; 31: 195-204.

Brandt J.T., Payne C.D., Wiviott S.D. et al. A comparison of prasugrel and clopidogrel loading dose on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J* 2007;153:9-16

Wiviott, SD, Braunwald E, McCabe DH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001-15.

# Thromboprophylaxis with antiplatelet agents



## **Problem Directed Anticoagulation**

The evidence is that the thrombogenicity of aortic mechanical valves is due to platelet activation:

Clopidogrel – ASA – achieve blockade of platelet activation.  
The coagulation process is blocked at the origin.  
Prasugrel-ASA has the same effect.

Warfarin – Has no effect on platelet activation and affects an already activated coagulation cascade.

# Thromboprophylaxis with antiplatelet agents



## **Historical Summary:**

### I. Use of antiplatelet agents in patients with mechanical aortic prostheses.

#### A. Use of dipyridamole alone or in combination with aspirin in patients with St. Jude Valves.

1. Hartz R.S., LoCicero III, J Kucich V et al: Comparative study of warfarin versus antiplatelet therapy in patients with a St. Jude Medical valve: The Aortic Position. J Thorac Cardiovasc Surg 1986; 92: 684-690.
2. Ribeiro PA, Al Zaibag MA, Idris M et al: Antiplatelet drugs and the incidence of thromboembolic complications of the St. Jude Medical aortic prostheses in patients with rheumatic heart disease. J Thorac Cardiovasc Surg 1986; 91:92-98.

“Aspirin plus dipyridamole is adequate for mechanical aortic valves, warfarin may be needed in patients with a mitral valve...”

3. Rao, PS, Solymar L, Mardini MK, et al. Anticoagulation therapy in children with prosthetic valves. Ann Thorac Surg 1989; 47: 582-92.

The studies demonstrated that platelet activation inhibition with dipyridamole and aspirin could reduce the thrombogenicity of prosthetic valves. However, the inclusion of patients with mitral prostheses in the results frequently confused the results. The idea that platelet inhibitors could reduce thrombogenicity was never accepted.

# Thromboprophylaxis with antiplatelet agents



## **Historical Summary** (cont).

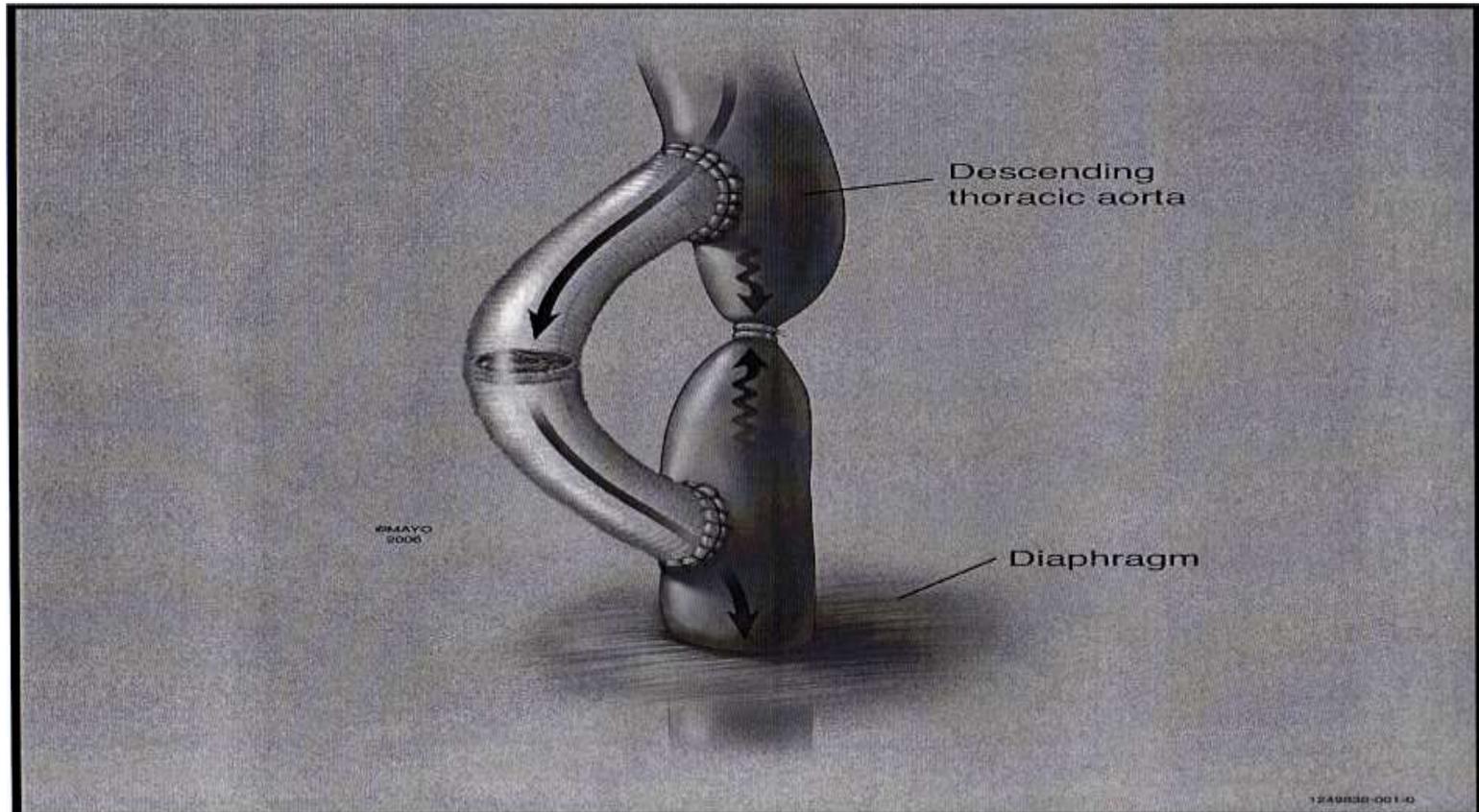
### II. Use of Aspirin plus warfarin in patients with mechanical aortic and mitral prostheses.

Turpie AGG, Gent M, Laupacis A et al: Comparison of aspirin with placebo in patients treated with warfarin after heart valve replacement. *N Eng J Med* 1993; 329: 524-529.

Turpie demonstrated a statistically significant reduction in embolic episodes from 8.5% to 1.9% in patients treated with warfarin plus aspirin versus patients with warfarin plus placebo.

# Thromboprophylaxis with antiplatelet agents

## Experimental model in swine



Mckellar SH, Thompson III, JL., **Garcia-Rinaldi R**, MacDonald RJ, Sundt III TM, Schaff HV. Short and long-term efficacy of aspirin and clopidogrel from thromboprophylaxis for mechanical heart valves: an In-Vivo study in swine. J Thorac Cardiovasc Surg. 2008 Oct; 136(4):908-14.

# Thromboprophylaxis with antiplatelet agents



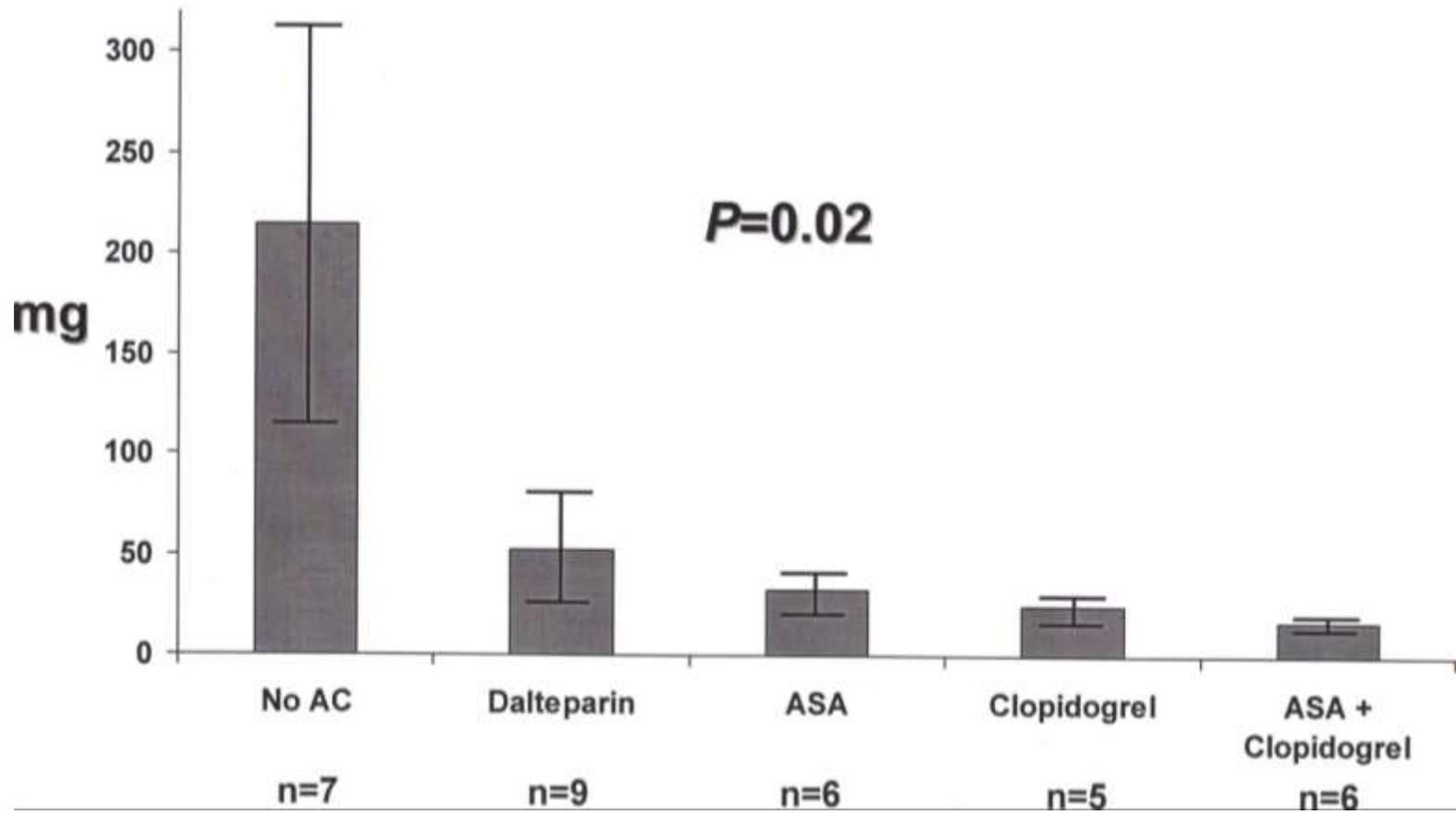
## Experimental Model in swine

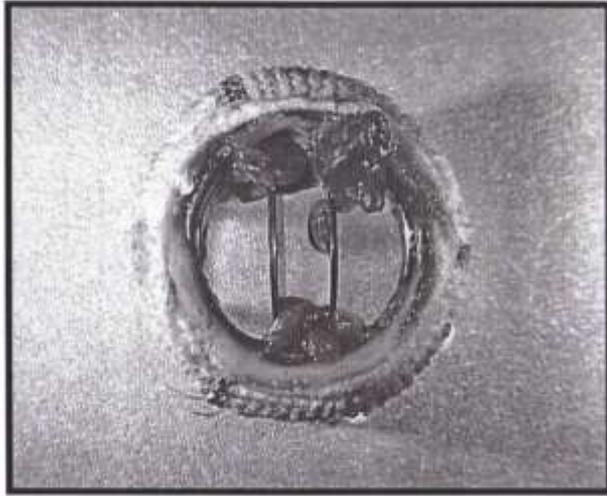
Agents used for thromboprophylaxis

1. Dalteparin (surrogate for warfarin)
2. Aspirin
3. Clopidogrel
4. Clopidogrel and aspirin

Animals sacrificed at 30 and 150 days. Amount of thrombus formed at the valve was weighed.

Mckellar SH, Thompson III, JL., **Garcia-Rinaldi R**, MacDonald RJ, Sundt III TM, Schaff HV. Short and long-term efficacy of aspirin and clopidogrel from thromboprophylaxis for mechanical heart valves: an In-Vivo study in swine. J Thorac Cardiovasc Surg. 2008 Oct; 136(4):908-14.0





**A**



**B**

## **Conclusion**

Antiplatelet therapy with clopidogrel and aspirin was more effective than heparin in preventing thrombus formation in this experimental model.

# Thromboprophylaxis with antiplatelet agents



Assays we utilize to determine degree of platelet reactivity and identify patients with clopidogrel resistance

1. Accumetrics Verify Now® - Point of- care light aggregometry – measures degree platelet reactivity
2. Thromboelastography – Platelet Mapping measures:
  - a. Degree of platelet inhibition
  - b. Platelet function in the presence of antiplatelet agents
  - c. Specific effect of antiplatelet agent
  - d. Clot strength

Results of platelet reactivity may be different between assays; however patients perform consistently in each assay

# Thromboprophylaxis with antiplatelet agents



## Clinical Study

- April 2001 to Present: 159 months (13.25 years)
- Measurement of Platelet Reactivity
  - 1) Accumetrics® Verify Now, Nov 2006
  - 2) Thromboelastography – Platelet Mapping 2007
- Availability of prasugrel September 2009

# Thromboprophylaxis with antiplatelet agents



## Patient Inclusions:

1. Resection of the ascending or transverse arch of the aorta.
2. Coronary Artery Bypass.
3. Mitral Valve repair including Geoform ring implantation.
4. Endarterectomy of the ascending aorta.
5. Resection of left ventricular aneurysm.
6. Enlargement of the aortic root with autologous pericardium.
7. Patients with Re-do cardiac interventions
8. Patients who need urgent peripheral vascular interventions.

# Thromboprophylaxis with antiplatelet agents



## Patient Exclusions:

1. Patients who require mitral valve replacement.
2. Patients in chronic atrial fibrillation.
3. Previous history of deep vein thrombosis, pulmonary embolism or any suggestion of hyper coagulability.
4. Previous history of CVA.

Patients with a history of bleeding duodenal ulcer are treated with highly selective vagotomy. Similar therapy is given patient presents with bleeding peptic ulcer disease after valve replacement.

# Thromboprophylaxis with antiplatelet agents

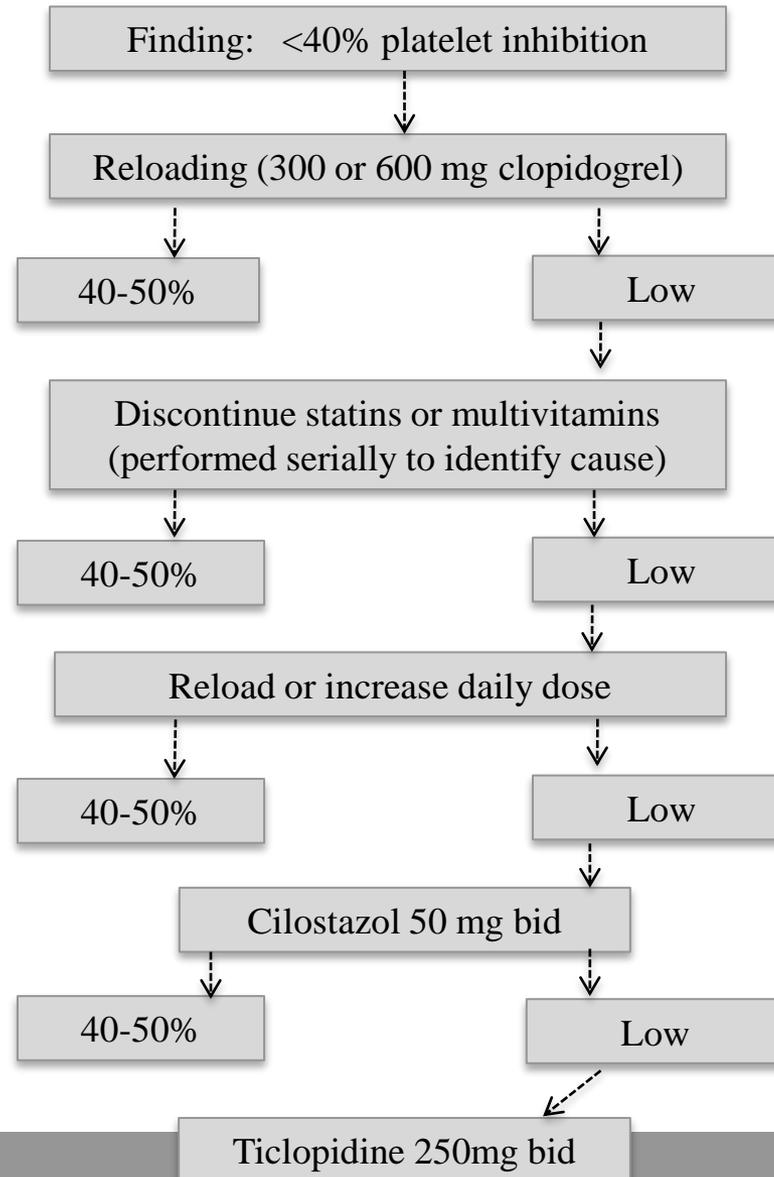
## Initial Anticoagulation Protocol:

- |                      |   |                           |
|----------------------|---|---------------------------|
| a. Clopidogrel 300mg | } | <b>the day of surgery</b> |
| b. Aspirin 325mg     |   |                           |
| c. Clopidogrel 75mg  | } | <b>daily</b>              |
| d. *Aspirin 81mg     |   |                           |

**Target degree of platelet inhibition: >40-50%**

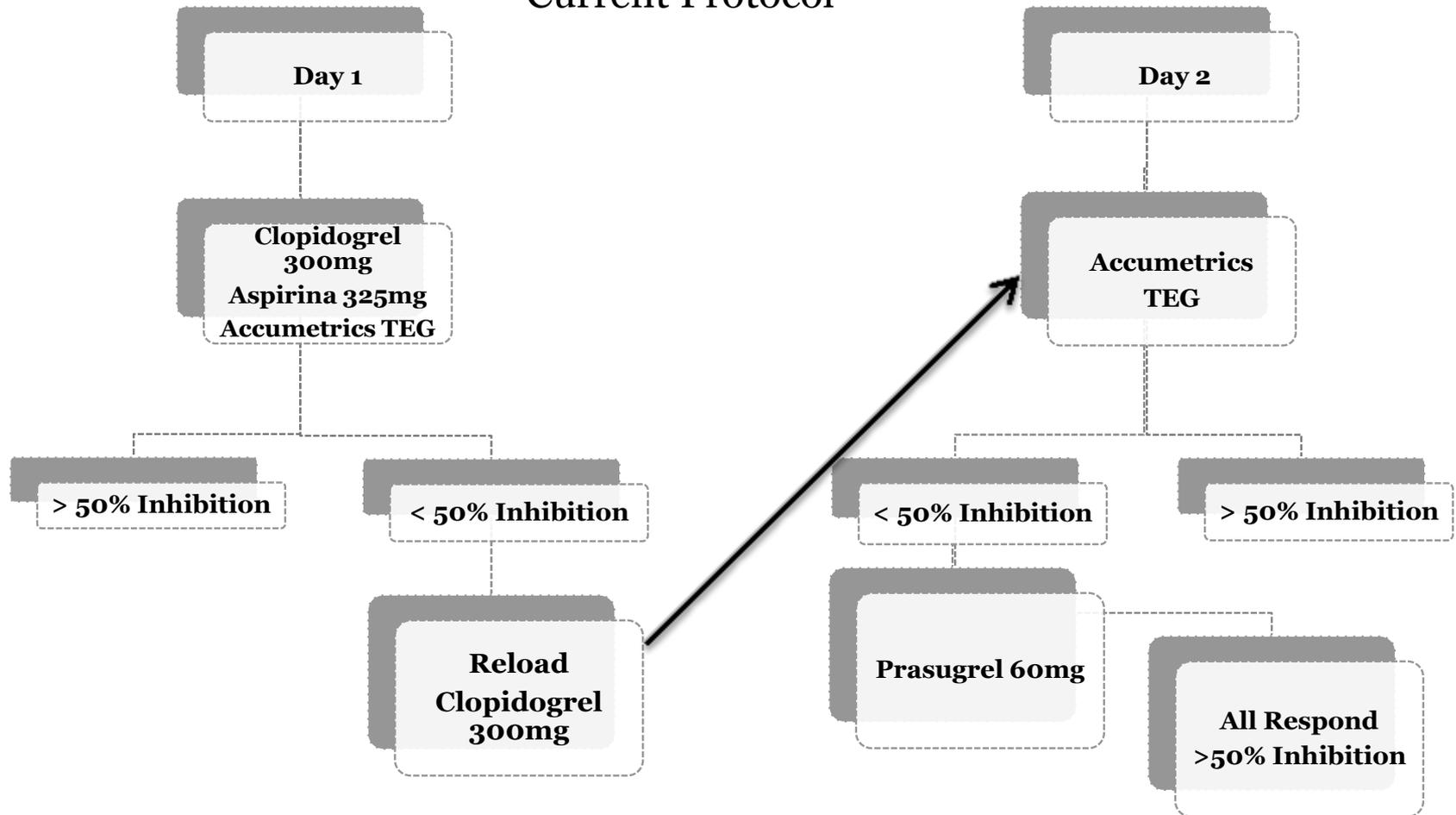
**From 2006 to 2009 clopidogrel resistance was treated using a complex pharmacologic algorithm.**

# Management of Clopidogrel Resistance (Prior to September 2009)



# Thromboprophylaxis with antiplatelet agents

## Current Protocol



Maintenance: Clopidogrel 75mg + 81mg ASA or Prasugrel 10mg + 81mg ASA

# Thromboprophylaxis with antiplatelet agents



## **Follow up**

1. Monthly clinic visits
2. Echocardiogram within 1 month post valve implantation and every six months
3. Accumetrics Verify Now® assay for degree of platelet inhibition
4. Thromboelastography® (TEG) platelet mapping to measure degree of platelet inhibition and clot strength.

Our goal: >40-50% platelet inhibition

# Thromboprophylaxis with antiplatelet agents



## Patient Characteristics

- ❖ Age: 64.2 ± 11.7 yrs. (21- 85yrs.)
- ❖ Gender: 141 males (64.1%)  
79 females (36%)  
Total 220 patients

## Incidence of Comorbidities

- a. Diabetes: 95/220 (43.2%)
- b. Hypertension: 157/220 (71.4%)
- c. Diabetes &  
Hypertension: 76/220 (34.5%)

# Thromboprophylaxis with antiplatelet agents

## Operations performed

Operation	# patients
AVR	220
AVR + Coronary Artery Bypass	88
AVR + Resection of Ascending Aorta and Coronary reimplantation	14
AVR + Enlargement of Aortic Root with autologous pericardium	9
AVR + Mitral Valve Repair	6
AVR (Redo)	5
AVR + hemiarch replacement	1
AVR + Coronary Artery Bypass + Endarterectomy of the Ascending Aorta	1
AVR + Alfieri Mitral Valve Repair + Resection of LV Aneurysm	1
AVR + Endarterectomy of Profunda femoral artery and femoro-femoral bypass	1

# Thromboprophylaxis with antiplatelet agents

## **Aortic Prostheses utilized**

Size	# Patients
16mm	9
17mm	8
18mm	4
19mm	94
20mm	1
21mm	62
23mm	29
25mm	12
27mm	1

# Thromboprophylaxis with antiplatelet agents



## Follow up

Mean follow up period: 47.0 months (3.9 years)

Total months at risk: 10108.1 (equivalent =  
842.4 patient-years)

# live patients

107

127

time post operative

> **5** year

> **3** years

# Thromboprophylaxis with antiplatelet agents

## Complications

Complication	# patients
Atrial Fibrillation	7
Low Cardiac Output	2
Atrial Flutter-bradycardia	2*
Painful, retained temporary pacing	2
Post operative Bleeding	1
Conduit Endocarditis	1
Valvular Endocarditis	1
Pulmonary Aspiration	1
Hypercoagulable state	1
Unable to prolong platelet inhibition	1
Thrombophlebitis	1
Paravalvular leak (Had a AVR elsewhere)	1
Mitral Regurgitation (Non operable)	1

# Thromboprophylaxis with antiplatelet agents



## **Bleeding Complications:**

Major bleeding 11 patients (5%) (1.3%/pt-yr)

- a. 9 GI bleed (6 required transfusions)
- b. 2 Sub arachnoid hemorrhage (cerebral aneurysm)

Akins C.W., Miller D.C., Turina M.I., et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. *Ann Thorac Surg* 2008;85:1490-5.

# Thromboprophylaxis with antiplatelet agents

## Deaths during the study period

**Total Deaths: 39 (17.7%)**

**Medical Deaths: 36 (16.1%)**

Cause	Number of patients
Myocardial Infarction	14 (36%)
Pulmonary Failure	6 (15%)
Aspiration pneumonia	3 (8%)
Endocarditis*	2 (5%)
Hemorrhagic stroke	2 (5%)
Perinephric abscess failure	1 (3%)
Pannus formation*	1 (3%)
Liver Disease	1 (3%)
Perinephric abscess	1 (3%)
Liver Disease	1 (3%)
Ischemic Stroke*	1 (3%)
Sepsis	1 (3%)
Cardiac Arrest after Carotid Endarterectomy	1 (3%)
Cardiac Arrhythmia not valve related	1 (3%)
Head trauma	1 (3%)
Drug Abuse	1 (3%)
Car Accident	1 (3%)

\*valve related mortality 4/220 = 1.8% (0.5% pt-yr)

# Thromboprophylaxis with antiplatelet agents

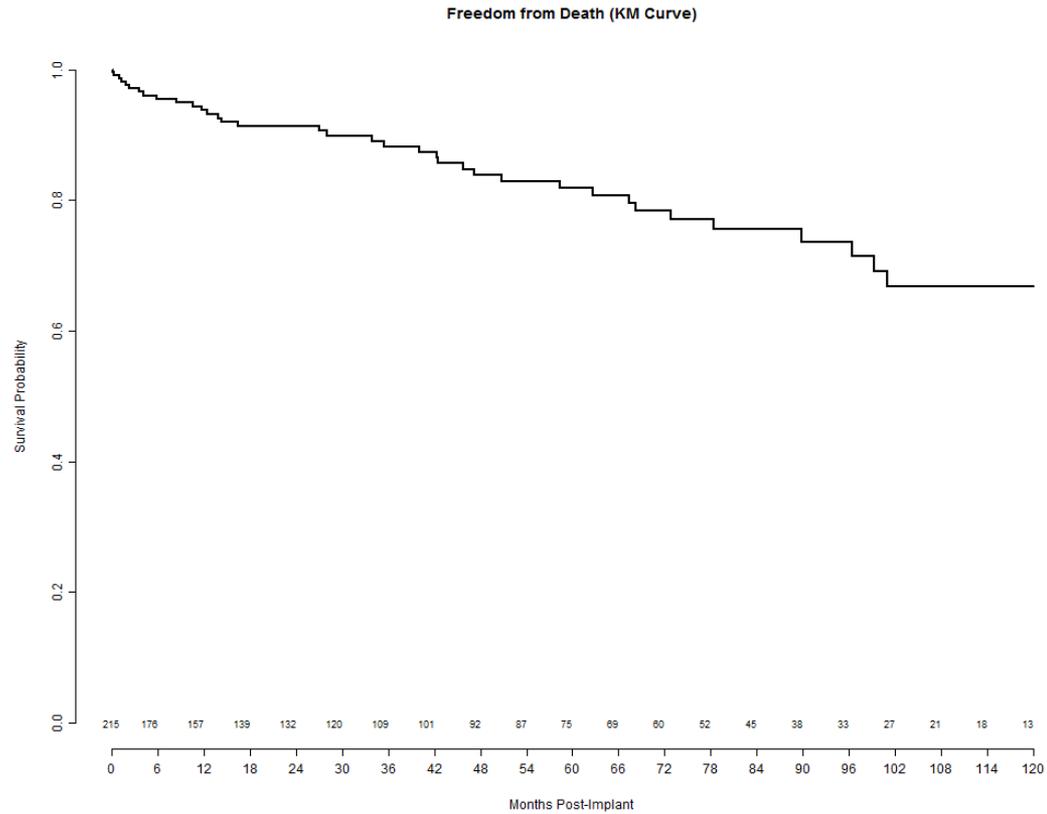


## Summary of Results

1. Non structural Dysfunction (PANNUS): 1/220
2. Valve related mortality: (1 conduit recurrent endocarditis, 1 prosthesis endocarditis, 1fatal ischemic stoke) 3/220
3. Thirty day Mortality: 0.6%

# Thromboprophylaxis with antiplatelet agents

## Kaplan-Meier Curves



# Thromboprophylaxis with antiplatelet agents



## Embolic Complications:

### A. TIA

- |   |   |
|---|---|
| 1. TIA of unknown etiology (reponder to Plavix)         | 1 |
| 2. TIA in a “cluster” (stopped clopidogrel and aspirin) | 1 |

**TOTAL** **2 (0.9%)(0.2 pt-yr)**

### B. ISCHEMIC STROKE

- |  |   |
|--|---|
| 1. patient <u>assumed</u> to be responder to clopidogrel | 1 |
| 2. Patients off Plavix                                   | 5 |
| 3. Patient non responders to Plavix                      | 1 |

**TOTAL** **7 (3.2%)(0.8 pt-yr)**

**Of these 7 patients, 6 (85%) were off Plavix or were non responders**

### C. HEMORRHAGIC STROKE

2

# Thromboprophylaxis with antiplatelet agents



## Strokes and TIAs: relationship to period of study

Period 1 (2001- August 2006) Before availability of assays

- a. **TIA**  $1/95 = 1.1\% = 0.1\%/pt\text{-yr}$
- b. **Strokes**  $5/95 = 5.3\% = 0.6\%/pt\text{-yr}$

Period 2 (August 2006-Present) After availability of assays

- a. **TIA**  $1/125 = 1.7\% = 0.1\%/pt\text{-yr}$
- b. **Strokes \***  $2/125 = 3.4\% = 0.2\%/pt\text{-yr}$

\*1 stroke in patient non responder to clopidogrel

\*1 stroke in patient who discontinued clop-ASA

**Since December 7, 2007 to present (6.5 years) none of the patients with mechanical aortic prostheses on the antiplatelet protocol has had a stroke or TIA.**

# Thromboprophylaxis with antiplatelet agents



## Conclusions

1. Thromboembolic events in patients with aortic mechanical prostheses are due to platelet activation and aggregation.
2. Effective platelet inhibition with antiplatelet agents clopidogrel and aspirin, or prasugrel and aspirin in clopidogrel hyporesponders, offers protection from thromboembolism.
3. This hypothesis was tested in a swine model, using St. Jude Mechanical aortic valves. Animals treated with clopidogrel and aspirin formed the least amount of clot, even less than that obtained with heparin.

# Thromboprophylaxis with antiplatelet agents



## Conclusions (cont.)

4. 220 consecutive patients with either St. Jude, OnX or ATS aortic mechanical prostheses were treated with clopidogrel and aspirin as sole anticoagulants.  
57 % of these patients had an aortic or other concomitant procedure.
  - a. 39 patients died: 4 of valve related causes (endocarditis, stroke, pannus formation).
  - b. 5% (1.3% pt-yr) of patients bled
5. Two patients had transient ischemic episodes (TIA) due to carotid stenosis. Both had carotid endarterectomy and resolved the problem.

# Thromboprophylaxis with antiplatelet agents



## Conclusions (cont.)

### 6. Nine patients had neurological events.

- a. Two patients (0.9%) (0.2% pt-yr) had TIAS. 1 in a clopidogrel responder with >50% platelet inhibition. 1 in a patient who had stopped taking the clopidogrel and aspirin (“cluster” TIAS).
- b. Seven patients (3.2%) (0.8% pt-yr) had an ischemic stroke
  1. 1 stroke in a patient assumed to be a clopidogrel responder (48.5 mo after AVR)
  2. Remaining 6 patients:
    - i. 1 non responder to clopidogrel.
    - ii. 5 had stopped taking clopidogrel-Asa.
      - a. 3 were taken off clopidogrel by their physician
      - b. 2 patients stopped clopidogrel by their own decision.

**6/7 strokes (85%) (0.7% pt-yr) occurred in patients who had discontinued clopidogrel and ASA or were not responsive to clopidogrel.**

- ### 7. Incidence of stroke decreased from 2.5%/pt-yr to 0.8%/pt-yr after acquiring the Accumetrics and TEG assays.

# Thromboprophylaxis with antiplatelet agents



## Conclusions (cont.)

8. Relationship of strokes to period of study
  - a. Period #1- Before assays: 5 (0.6%/pt-yr)
  - b. Period #2 - After assays: 2\* (0.2%/pt-yr)  
\*One stroke occurred in a patient non responsive to clopidogrel and the other one in a patient off clop-ASA.

**Since December 7, 2007 to present (6.5 years) none of the patients with mechanical aortic prostheses on the antiplatelet protocol has had a stroke or TIA.**

9. Measurement of platelet reactivity allowed us to identify patients not responsive to clopidogrel, hyporesponders and those who had stopped the medication. Identification of the patients led to a closer follow up and rapid resolution of platelet inhibition <40%, usually due to poor patient compliance.

# Thromboprophylaxis with antiplatelet agents



## Conclusions (cont.)

10. Three patients that had strokes who taken off clopidogrel-ASA by their physician were restarted on Clop-ASA after 2D echo exam of the valve and left atrium. They have not experienced thromboembolic events.
11. There were no cases of valve thrombosis or peripheral thromboembolism
12. Non or hypo responsiveness to clopidogrel were aggressively treated prior to the availability of prasugrel.
  - a. Statin or discontinuation of vitamin preparations,
  - b. administration of cilostazol
  - c. Taking with ticlopidine. These patients required monthly monitoring and frequent reloading with clopidogrel due to increased platelet reactivity.

# Thromboprophylaxis with antiplatelet agents



## Conclusions (cont.)

13. Prasugrel is now utilized in hyporesponders with immediate resolution and increase in the degree of platelet inhibition.
14. Current requirements for thromboprophylaxis with antiplatelet agents in patients with mechanical prostheses:
  - A) Measure the degree of platelet inhibition.
  - B) Identify patients who are non or suboptimal responders to Clop-ASA.
  - C) Poorly compliant or patients need dosage modification.
  - D) Poor responders: Prasugrel.
  - E) Non responders to clopidogrel: prasugrel
15. Some patients with low platelet inhibition to clopidogrel but response to aspirin did not have strokes. This is suggestive that the combination of a satisfactory platelet inhibition by aspirin, coupled with any degree of platelet inhibition due to clopidogrel, acts in synergistic manner to offer protection from thromboembolic events.  
Prasugrel offers the same degree of thromboprophylactic protection as clopidogrel.
16. A prospective randomized study versus warfarin, will determine the superiority of warfarin or antiplatelet therapy.