

Cardiovascular Pharmacology: A Clinical Update on Today's Drugs and Tomorrow's Promise

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Agenda

- Antiplatelet vs. Anticoagulant
 - White Clot or Red Clot
- Atrial Fibrillation
 - Warfarin vs. Aspirin
 - Cardioversion, Managing an Elevated INR, & Bridging
- Antiplatelet Therapy – Who and How Long?
- New FDA Approved CV Drugs of 2007
- Cardiovascular Drugs of the Future

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Arterial and Venous Thrombi

Arterial thrombi (white clots)

- Occur in areas of elevated shear stress
- Form at sites of vascular injury and disturbed blood flow
- Composed predominately of platelets

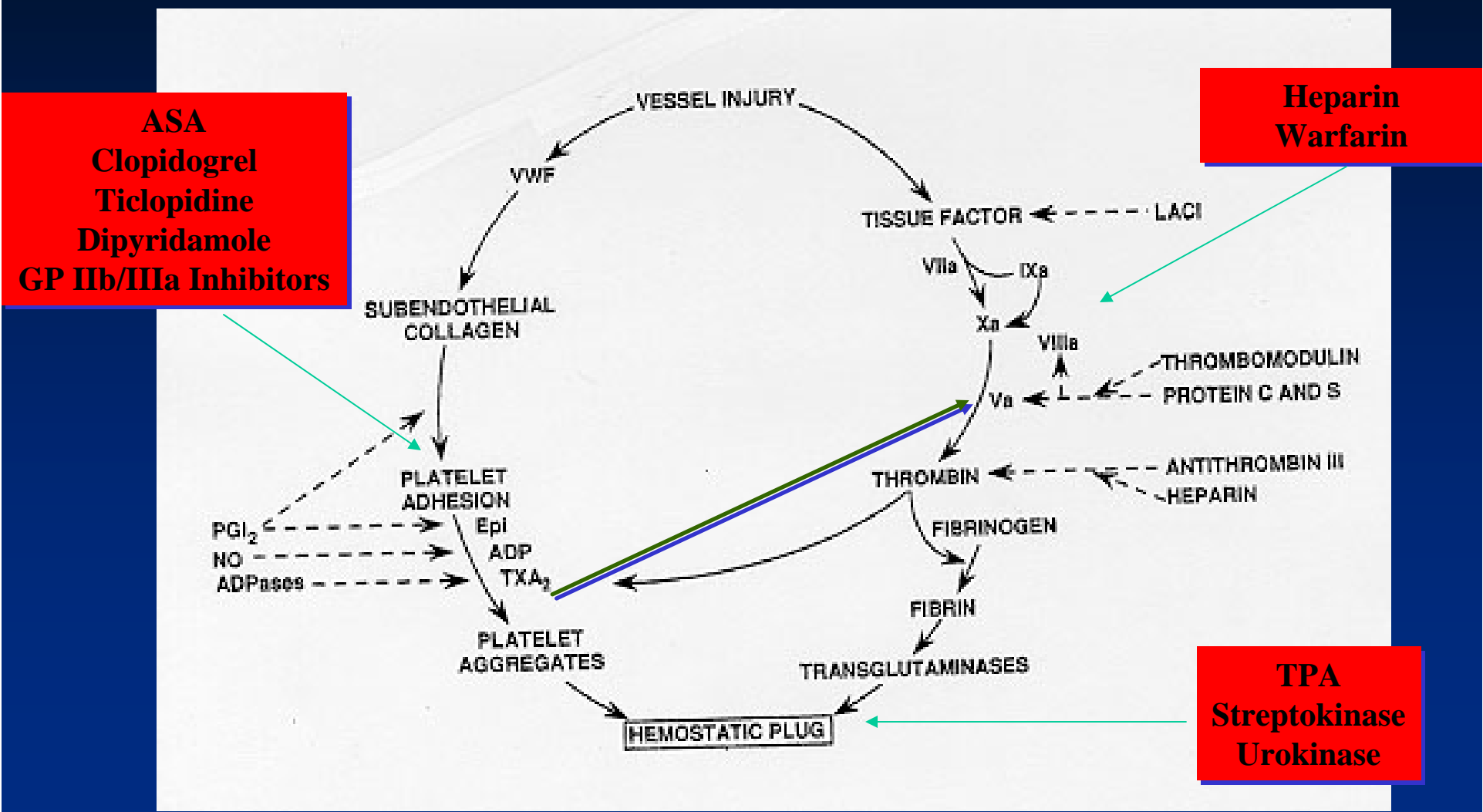
Arterial and Venous Thrombi

Venous thrombi (red clot)

- Form either in response to venous stasis or vascular injury following surgery or trauma
- In areas of stasis, reduced blood flow prevents dilution of activated coagulation proteins
- Composed predominantly of red blood cells

Clotting Cascade

Adapted from Colman RW et al. Overview of Hemostasis. In: Colman RW ed. *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*. 3rd ed. Philadelphia, Pa: JB Lippincott;1994.



ACCP Recommendations for Warfarin as First-Line Therapy

- Mechanical heart valves
- Valvular heart disease
- Cardioembolic stroke
- Deep vein thrombosis and pulmonary embolism
- Atrial fibrillation

There is no benefit to using warfarin in patients with coronary artery disease except in patients who are at risk of having a mural thrombus post-MI.

a) True

b) False

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a) True

b) False

Anticoagulation in Patients with CAD

Anand & Yusuf conducted a meta-analysis of randomized trials in which oral anticoagulation was tested in patients with CAD for secondary prevention of CV events

- Data from over 20,000 patients included

Moderate (INR 2-3) or High Intensity OA (INR>2.8) vs. Control

- Moderate intensity OA showed a non-significant RRR of 16% for stroke, MI, or CVD but increased the risk of major bleeding by 7.7 fold
- High intensity OA significantly reduced the RRR of stroke, MI, or CVD by 43% but increased the risk of major bleeding by 4.5 fold (0.7% vs. 4.6%)

Anticoagulation in Patients with CAD

Moderate or High Intensity OA (INR>2.8) vs. Aspirin

- OA significantly reduced the RRR of stroke, MI, or CVD by 21% but increased the risk of major bleeding by 2.1 fold

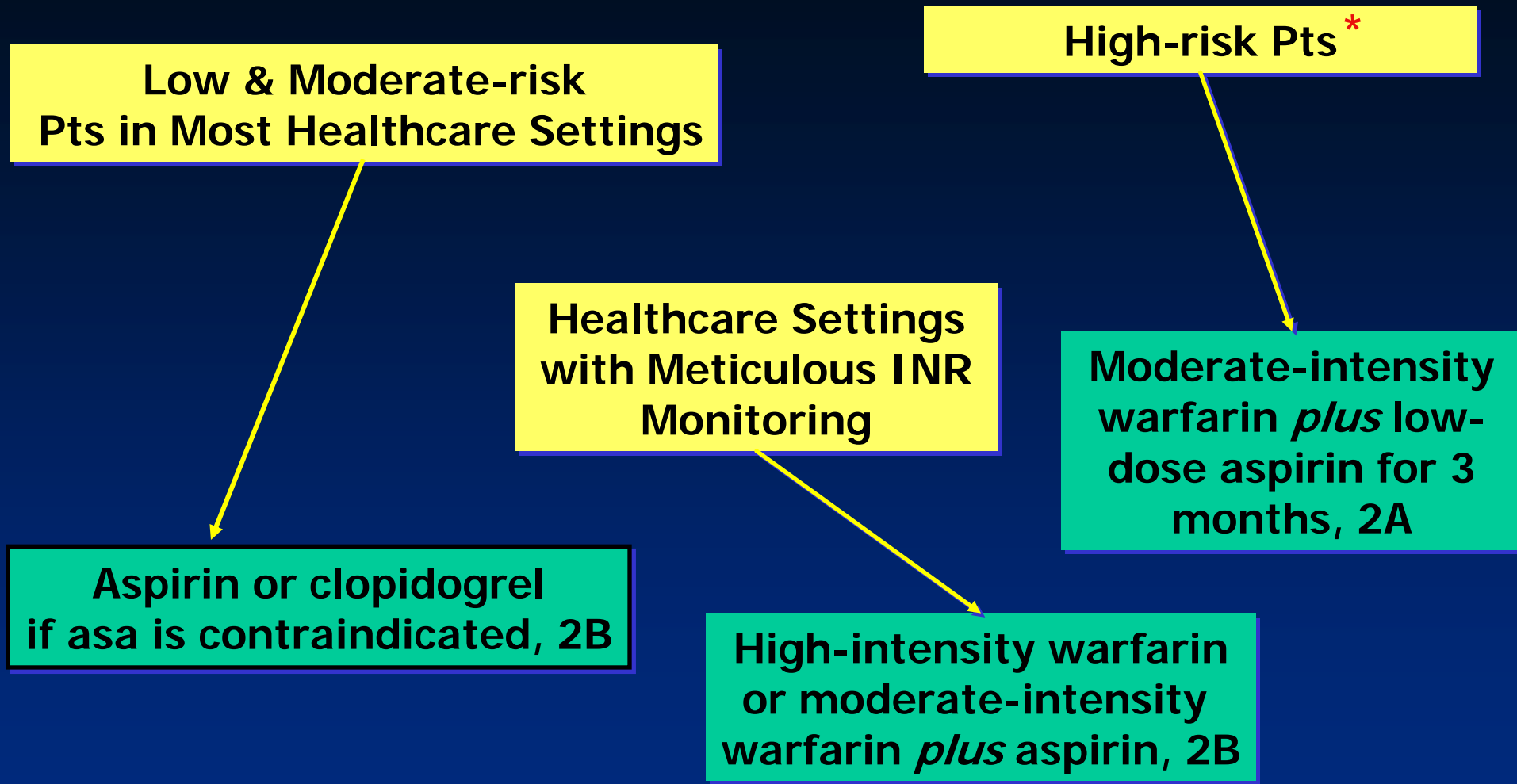
Moderate to High Intensity OA plus ASA vs. ASA alone

- Compared to aspirin, OA plus aspirin significantly reduced the RRR of stroke, MI, or CVD by 12% (12.6% vs. 15.9%) but increased the risk of major bleeding by a RRR of 74% (1.7% vs. 3.0%)

Low Intensity OA plus ASA vs. ASA alone

- No significant benefit of combination therapy vs. ASA alone
- A non-significant increase in major bleeding of 25% was seen with combination therapy compared to ASA alone

ACCP Recommendations Post MI



* High risk features include large anterior MI, significant heart failure, intracardiac thrombus, history of thromboembolism

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Atrial Fibrillation

- Most common cardiac rhythm disorder and is a significant independent risk factor for ischemic stroke
- About 2.5 million people in the United States have a-fib
- Prevalence of a-fib increases with age, affecting nearly 10% of people >80 years of age
- Based on the Framingham study, a-fib increases the risk of stroke about 1.5% in the age group 50 to 59 years and about 23.5% in the age group 80 to 89 years
- A-fib accounts for approximately 15% of all strokes in the US

Treatment of Atrial Fibrillation

- Warfarin
 - Compared to control, reduces the risk of stroke by a RRR of 68%
 - Compared to aspirin, reduces the risk of stroke by a RRR of 52%
- Aspirin
 - Compared to control, reduces the risk of stroke by a RRR of 21%

A “Black-Box Warning” was added to the package labeling of warfarin only in 2006.

a) True

b) False

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a) True

b) False

Why a Black-Box Warning?

- Office of Surveillance and Epidemiology of the FDA
 - Diane Wysowski, PhD and Colleagues
- FDA analyzed data on the use of warfarin and its prevalence of bleeding complications in the US
 - National Prescription Audit Plus database of IMS Health, AE reports submitted to FDA, deaths due to therapeutic use of anticoagulants from vital statistics data, and warfarin bleeding complications from national hospital ER department data

Why a Black-Box Warning?

- From 1998 to 2004
 - Outpatient warfarin prescriptions increased 45% from 21 million to nearly 31 million
- Warfarin was among the top 10 drugs with the largest number of serious AE reports submitted to the FDA during the 1990 and 2000 decades
- US death certificates showed anticoagulants ranked 1st in 2003 and 2004 in the number of total mentions in deaths for drugs causing "adverse effects in therapeutic use."

Why a Black-Box Warning?

- From 1999 to 2003, data from hospital ER departments indicated that warfarin was associated with about 29,000 visits for bleeding per year
- Major bleeding rates for warfarin are as high as 10% to 16%

All atrial fibrillation patients > 65 years old should be treated with warfarin unless there is the an absolute contraindication to warfarin therapy.

a) True

b) False

All atrial fibrillation patients > 65 years old should be treated with warfarin unless there is the an absolute contraindication to warfarin therapy.

a) True

b) False

Atrial Fibrillation – Who should get Warfarin?

Age	Risk Factors*	Recommendation
< 65 Years	Absent	Aspirin 325mg/day, Grade 1B, estimated benefit may not be worth the increased bleeding risk and burden of anticoagulation
65 to 75 Years	Absent	Warfarin (INR 2.5) or Aspirin 325mg/day are acceptable, Grade 1A, estimated benefit may not be worth the increased bleeding risk and burden of anticoagulation
> 75 Years	N/A	Warfarin (INR 2.5), Grade 1A

* Prior ischemic stroke, TIA, or systemic embolism, age >75 years, moderately or severely impaired left ventricular systolic function and/or congestive heart failure, history of hypertension, or diabetes mellitus.

Atrial Fibrillation – Elective Cardioversion

A-fib \geq 48 hours

- Warfarin (INR 2.5) for 3 wks before and 4 wks after cardioversion, Grade 1C, continuation beyond 4 wks is based on risk factors or paroxysmal atrial fibrillation (PAF)
- Anticoagulation (UFH PTT 60 or warfarin \geq 5 days INR 2.5) and multiplane TEE screening, if not thrombus and cardioversion successful, warfarin \geq 4 wks

A-fib $<$ 48 hours

- Cardioversion can be performed without anticoagulation but if no contraindications then IV heparin or LMWH (DVT treatment dose) is suggested at presentation, warfarin post-cardioversion only if risk factors

Managing a Supra-therapeutic INR

- INR above therapeutic but < 5 with no significant bleeding
 - Lower or omit dose and monitor more frequently, **Grade 2C**
 - If minimally above therapeutic, no dose reduce may be needed
- INRs ≥ 5 but < 9 with no significant bleeding
 - Omit 1 to 2 doses and monitor more frequently or omit 1 dose and give vitamin K1 1mg to 2.5mg orally, **Grade 2C**
 - If more rapid reversal is required, vitamin K1 ≤ 5 mg orally can be given, INR reduction can be expected to occur within 24 hrs, **Grade 2C**

Managing a Supra-therapeutic INR

- INRs ≥ 9 with no significant bleeding
 - Hold warfarin therapy and give vitamin K1 5mg to 10 mg orally, a substantial INR reduction can be expected in 24 to 28 hours, **Grade 2C**
 - Monitor more frequently and give more vitamin K1 if necessary
- In patients with serious bleeding and an elevated INR
 - Hold warfarin therapy and give vitamin K1 10mg by slow IV infusion which can be supplemented with FFP, prothrombin complex concentrate, or recombinant factor VIIa, **Grade 1C**
 - Vitamin K1 can be administered every 12 hours
- In pts with life-threatening bleeding and an elevated INR
 - Hold warfarin therapy and give prothrombin complex concentrate or recombinant factor VIIa supplemented with vitamin K1 10mg by slow IV infusion, **Grade 1C**

Patients Undergoing Invasive Procedures

- **Low risk patients**
 - Stop warfarin 4 days before surgery, use post-operative prophylaxis (if procedure increases thrombosis risk) with low dose UFH or prophylactic dose of LMWH and start warfarin simultaneously, Grade 2C
- **Intermediate risk patients**
 - Stop warfarin 4 days before surgery and begin pre-op prophylaxis 2 days before procedure with low dose UFH or prophylactic dose of LMWH followed post-operatively with low dose UFH (LMWH) and warfarin, Grade 2C

Patients Undergoing Invasive Procedures

- **High risk patients**
 - Stop warfarin 4 days before surgery, begin full dose UFH or LMWH as INR falls about 2 days preoperatively
 - UFH can be given SC on an outpatient basis and IV infusion after hospital admission and should be discontinued 5 hours before surgery
 - An alternative is to continue SC UFH or LMWH preoperatively and discontinue therapy 12 to 24 hours before surgery
 - Postoperatively, administer full dose UFH or LMWH and warfarin
 - Grade 2C
- **Dental procedures**
 - Control local bleeding with tranexamic mouthwash or epsilon aminocaproic acid mouthwash instead of interrupting anticoagulation therapy, Grade 2B

The Search to Replace Warfarin

Ximelagatran (Exanta, AstraZeneca)

- Not approved by FDA in September 2004
 - 6% of pts had significant liver-enzyme elevations
 - A suggestions of increased cardiac events
 - Margin of noninferiority between warfarin and ximelagatran of 2% use in SPORTIF trials too liberal

Aspirin *plus* Clopidogrel

- ACTIVE W – Compared aspirin *plus* clopidogrel to warfarin
 - Enrolled 6600 patients and followed for 2 year
 - Trial discontinued early due to superiority of warfarin over aspirin *plus* clopidogrel

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In patients with coronary artery disease, how long should they be treated with clopidogrel therapy?

- a) 1 month
- b) 6 months
- c) 9 months
- d) 1 year
- e) Indefinitely
- f) None of the above

In patients with coronary artery disease, how long should they be treated with clopidogrel therapy?

- a) 1 month
- b) 6 months
- c) 9 months
- d) 1 year
- e) Indefinitely
- f) **None of the above**

The Data Behind Clopidogrel

The Trials

- **CAPRIE – Clopidogrel vs. aspirin**
 - Pts with documented stroke, MI, or PAD receive treatment for up to 3 years, average 1.6 yrs
 - Clopidogrel significantly reduced the risk of stroke, MI, & CVD by a RRR of ~9%
- **CLASSICS – Clopidogrel & ASA vs. Ticlopidine & ASA**
 - Pts with CAD undergoing stent placement with a bare metal stent (BMS) were all treated for 30 days
 - Significantly fewer patients on C + A experienced bleeding complications, neutropenia, thrombocytopenia, or early discontinuation due to an AE
- **CURE – Clopidogrel & ASA vs. ASA alone**
 - Pts with ACS received treatment for up to 12 months, average 9 months
 - Combination therapy significantly reduced the risk of stroke, MI & CVD by a RRR of 20%

The Data Behind Clopidogrel

The Trials

- **PCI-CURE – clopidogrel & ASA vs. ASA alone**
 - Substudy of CURE, all pts with ACS received clopidogrel & ASA for 1 month following stent placement, one group continued with C + A while the other continued with ASA alone out to 12 months, average 9 months
- **CREDO – Clopidogrel & ASA vs. ASA alone**
 - All pts with stable & unstable angina following stent placement (BMS) received C + A for 1 month, one group continued with C + A while the other continued with ASA alone out to 12 months
 - Combination therapy significantly reduced stroke, MI, or death by a RRR of 27%
- **CHARISMA – Clopidogrel & ASA vs. ASA alone**
 - Pts with stroke, MI, PAD, or risk factors for CAD received treatment for an average of 28 months
 - Combination therapy reduced the risk of stroke, MI, or CVD by a RRR of 7.1% which was not statistically significant
 - Subgroup of pts with documented stroke, MI, or PAD had a benefit – RRR of 12%

How Long Should My Patient Be on Clopidogrel ?

Prevention of Stent Thrombosis

- Bare metal stent – minimum of 2 weeks but ideally 1 month
- Drug-Eluting Stents
 - Cypher stent – Minimum of 3 months
 - TAXUS stent – Minimum of 6 months
- Drug-Eluting Stents and Late Stent Thrombosis
 - FDA panel on late stent thrombosis recommends clopidogrel and aspirin therapy for at least 12 months in patients getting a drug-eluting stent

How Long Should My Patient Be on Clopidogrel?

Secondary Prevention of Cardiovascular Events

- Acute Coronary Syndrome
 - Up to 12 months per ACC/AHA guidelines
- Post Stenting With a Bare Metal Stent
 - Up to 12 months
- Documented atherosclerosis with stroke, MI, or PAD
 - Up to 3 years with clopidogrel alone

Safety of Clopidogrel Long-term?

- **CAPRIE - No significant difference in bleeding between clopidogrel & ASA**
 - GI Hemorrhage: Clopidogrel 2% vs. ASA 2.7%
 - Intracranial Hemorrhage: Clopidogrel 0.4% vs. ASA 0.5%
- **CURE – Bleeding significantly increased with clopidogrel & ASA compared to ASA alone**
 - Minor bleeding: C + ASA 5.1% vs. ASA alone 2.4%
 - Major bleeding: C + ASA 3.7% vs. ASA alone 2.7% - no difference in intracranial hemorrhage
 - Major bleeding increases with aspirin dose: C + ASA <100mg 2.6% vs. ASA 2%, C + ASA >200mg 4.9% vs. ASA 4%
- **CREDO – No significant difference in bleeding**
- **CHARISMA – No significant difference in GUSTO severe bleeding but moderate bleeding was increased**
 - Fatal bleeding and intracranial hemorrhage – No difference
 - Moderate bleeding: C + ASA 2.1% vs. ASA 1.3%, $p < 0.001$

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New CV Drugs of 2007

- Aliskiren (Tekturna[®])
- Protein C (Ceprocin[®])

New CV Drugs of 2007

- **Aliskiren (Tekturna[®]) – Unscored 150mg & 300mg tablet**
 - Direct renin inhibitor
 - Indicated for the treatment of hypertension either alone or in combination with other agents
 - Dosing: 150mg to 300mg daily, doses above 300mg provide no additional BP reduction
 - BP reduction: 9-13/8-10 mmHg with 150mg, 14-15/11-12 mmHg with 300mg
 - Most common side effect is diarrhea, occurring in 2.3% of pts on 300mg, experience more frequently by women & the elderly ≥ 65 yrs
 - AUC is reduced by about 70% if taken with high fat meal
 - Metabolized by CYP 3A4, irbesartan reduces C_{max} by 50%, ketoconazole increases C_{max} by 80% and atorvastatin by 50%
 - Cost: 150mg for 1 month ~\$70 and 300mg for 1 month ~\$90

New CV Drugs of 2007

- **Protein C (Ceprotin®)– Single dose powder vials of 500 IU & 1000 IU human protein C**
 - Protein C is a precursor of a vitamin K-dependent anticoagulant glycoprotein that has potent anticoagulant effects
 - Made from human plasma
 - Indicated for the treatment of severe congenital protein C deficiency for the prevention and treatment of venous thrombosis and purpura fulminans
 - Dosing: Acute episode – 100-120 IU/kg then 60-80 IU/kg Q6 hours x 3 doses, and 45-60 IU/kg Q12 hours for prophylaxis
 - Most common side effect is itching and rash

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**The estimate cost of getting a drug
FDA approved and to the market is:**

- a) \$350 Million
- b) \$500 Million
- c) \$615 Million
- d) \$750 Million
- e) \$802 Million

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CV Drugs of Tomorrow

Drug	Mechanism of Action	Potential Indications	Anticipated Approval
Torcetrapib (Pfizer)	CETP inhibitor that raises HDL by as much as 50%, some pts may experience elevations in SBP	Low HDL, CV disease prevention	Research terminated due to higher risk of death & CV events in ILLUMINATE, failed to show regression of atherosclerosis in RADIANCE 2
Dabigatran (BI)	Direct thrombin inhibitor, dosed once to twice daily	AF, VTE prophylaxis and treatment	2009, RE-NOVATE similar efficacy & safety in HR to enoxaparin 40mg, RE-MOBILIZE equivalence not met in KR for VTE & death in comparison to enoxaparin 60mg
Rivaroxaban (JNJ & Bayer)	Factor Xa inhibitor	VTE prophylaxis & treatment	2009, RECORD 3 superior efficacy in KR to enoxaparin 40mg

The search to replace warfarin continues!!!

CV Drugs of Tomorrow

Drug	Mechanism of Action	Potential Indications	Anticipated Approval
Idraparinux (SA)	Factor Xa inhibitor, long half-life, dosed once weekly	VTE prophylaxis and treatment, AF	2009, Van Gogh trials show equivalence to standard therapy in DVT but not in PE
ApoA-1 Milano (Pfizer)	Variant form of HDL discovered in a small group of people in a Italian village	Dyslipidemia and atherosclerosis regression	Research ongoing but initial studies are promising, needs to be given as IV infusion
Prasugrel (Lilly/Sankyo)	ADP inhibitor, thought to be more potent than clopidogrel	ACS, MI, stroke prevention	Late 2008, TRITON TIMI 38 comparing Clopidogrel to Prasugrel in ACS pts set for presentation at AHA 2007
Rimonabant (SA)	Cannabinoid receptor antagonist	Weight loss, metabolic syndrome	FDA advisory panel voted against approval due to an increased risk of neurological & psychiatric side effects

Questions & Discussion