Anti-platelet therapy and Peripheral Arterial Disease

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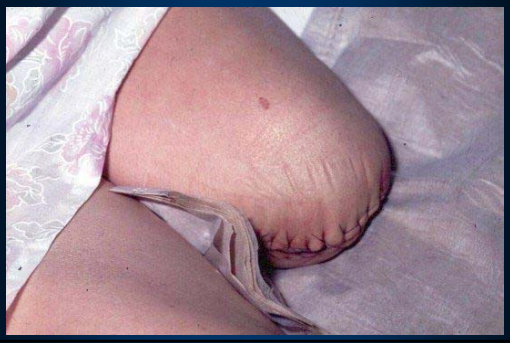
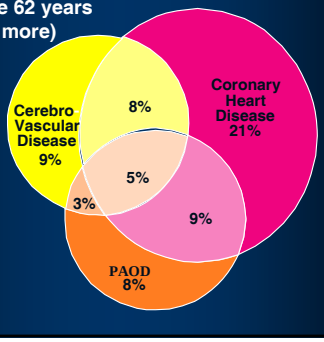
University of Aberdeen

Peripheral Arterial Disease

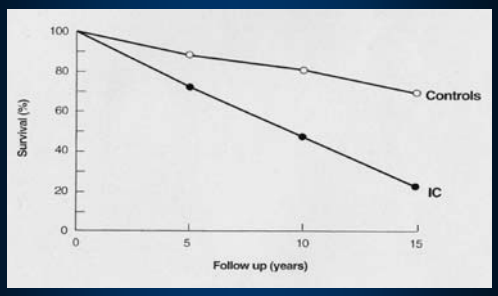


Peripheral Arterial Disease

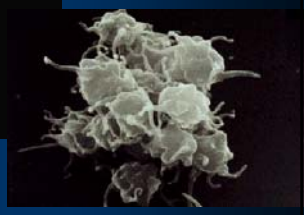
Population above 62 years (63% had one or more)



Mortality



PLATELETS



REVIEW

The Role of Platelets in Peripheral Vascular Disease

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Platelets play a major role in acute ischaemic syndromes and peripheral vascular disease. They are involved in the development and progression of atherosclerosis, native vessel and graft thrombosis. They have a central role in the development of restenosis and reocclusion after peripheral percutaneous transluminal angioplasty. Antiplatelet therapy has been shown to be beneficial in patients undergoing peripheral vascular surgery or radiological intervention. Yet current routine therapy, namely aspirin and dipyridamole are limited in their mode of action and efficacy. Recent developments in the understanding of platelet function has led to the development of new more potent drugs such as clopidogrel. Combination of drugs and more specific investigation of individual platelet function may well result in improved bypass and angioplasty patency rates. The results of proposed large randomised controlled trials on the role and safety of aspirin and clopidogrel are awaited with interest. Given the importance of platelets in peripheral vascular disease highlighted in this review, achieving an optimal safe anti-platelet effect for each patient with peripheral vascular disease should be the target of future research.

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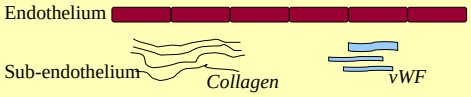
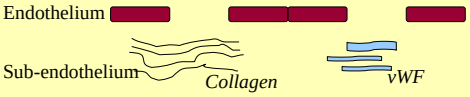
Rudolf Virchow
1821-1902

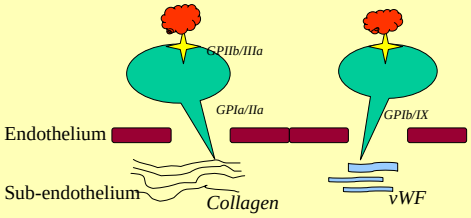
Endothelial Denudation



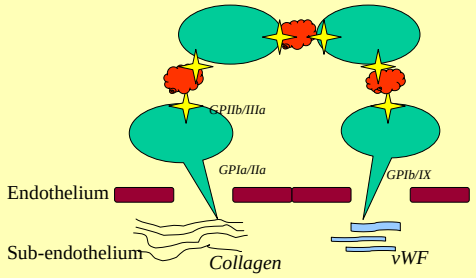
Endothelial Denudation



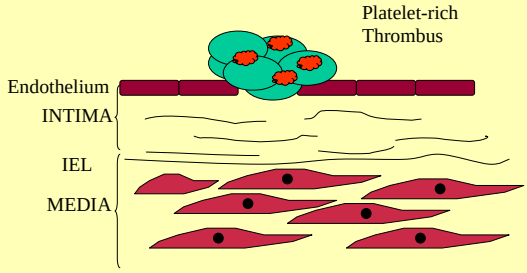
Platelet Adhesion



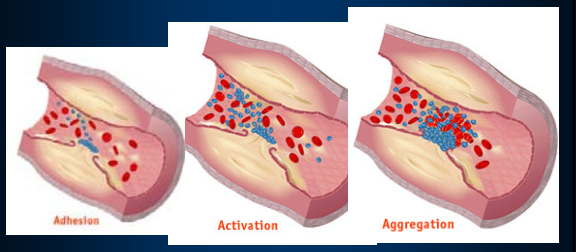
Platelet Aggregation



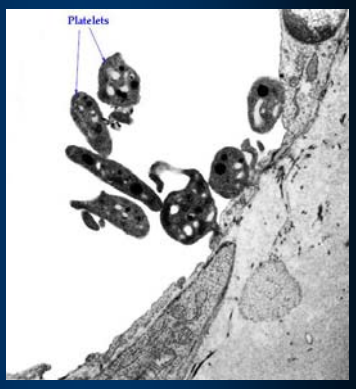
Platelet adhesion and aggregation



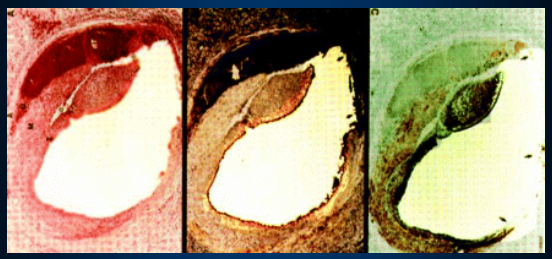
Vessel occlusion



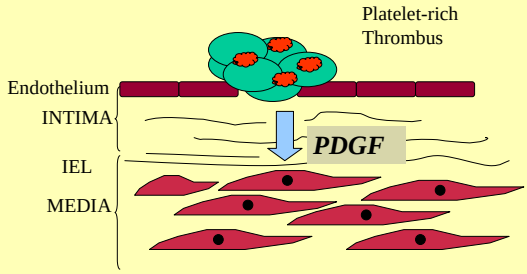
Graft Occlusion



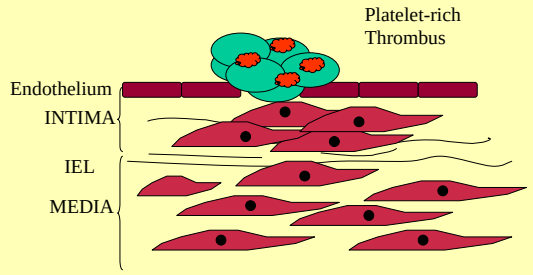
Angioplasty



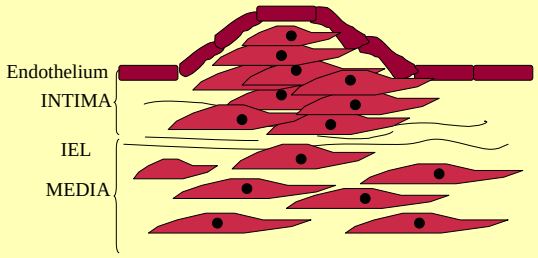
Platelet-Induced Smooth Muscle Proliferation



Platelet-Induced Smooth Muscle Proliferation



Platelet-Induced Smooth Muscle Proliferation



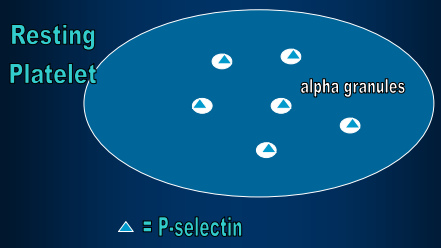
Platelet activation is increased in peripheral arterial disease

K. Cassar, MD, FRCS(Ed),[a] P. Bachoo, FRCS(Gen Surg),[a] L. Ford, PhD,[a] M. Greaves, MD, FRCP, FRCPath,[b] and J. Brittenden, MD, FRCS(Gen Surg),[a] *Aberdeen, Scotland*

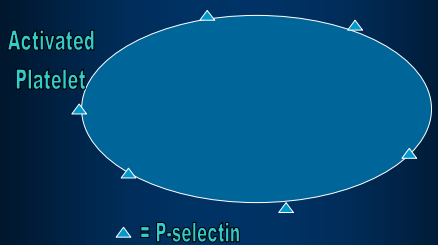
(J Vasc Surg 2003;38:99-103.)

- Observational study: controls, claudicants, criticals – 100 subjects
- P-selectin – marker of platelet activation

P-selectin

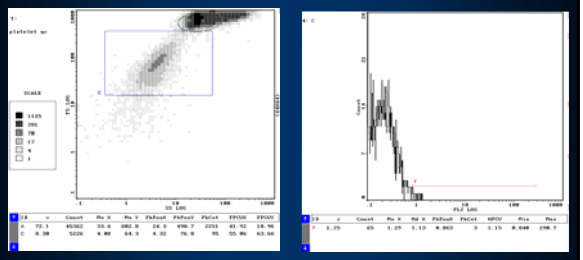


P-selectin

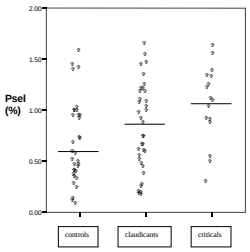


Flow Cytometer

Platelet activation- P-selectin

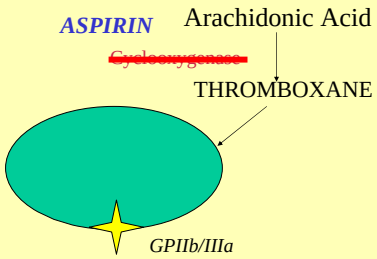


Results:P-selectin expression

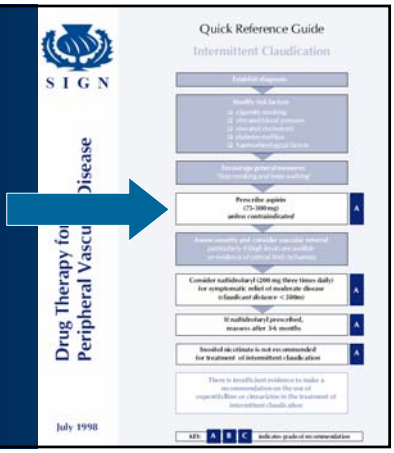


P-selectin expression (%)	
Controls	*0.59*
Claudicants	*0.85 (p=0.023)*
Criticals	*1.11 (p=0.028)*

Antiplatelet Drugs



SIGN 1998



Joint British recommendations: 1998

- Patients with PAD should be managed in the same way as those with established coronary heart disease

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REVIEW

Antiplatelet Therapy in Peripheral Arterial Disease. Consensus Statement

Peripheral Arterial Diseases Antiplatelet Consensus Group

Department of Vascular Surgery, Northern Vascular Centre, Freeman Hospital, Newcastle upon Tyne, U.K.

Objectives: Antiplatelet agents are commonly prescribed to reduce the risk of myocardial infarction, stroke and graft occlusion in patients with peripheral arterial disease (PAD). The objective was to summarise current evidence and provide recommendations on the use of antiplatelet agents in PAD.
Methods: A consensus group was assembled including 20 specialists from a variety of fields involved in the management of patients with PAD. Data was circulated in a systematic manner prior to a main consensus meeting held in November 2001. The document subsequently produced was circulated within the group to ensure agreement in the interpretation and presentation of its findings.
Results: Consensus recommendations are provided in 7 common or contentious scenarios in PAD. The recommendations are graded to reflect the evidence available and interpretations of the group. Although the document provides recommendations, it is stressed that they must be interpreted in the light of individual patient circumstances.
Conclusion: Antiplatelet agents have an important role in the management of patient with PAD. Although this document provides consensus recommendations, the optimum treatment in many scenarios remains unclear due to a lack of focused clinical trials in PAD.

Key Words: Antiplatelet therapy; Peripheral arterial disease; Vascular surgery; Angioplasty; Consensus.

Anti-thrombotic Trialists' Collaboration Meta-analyses (2002)

- 3123 patients with intermittent claudication in 26 trials

Category of trial	No of trials with data	No (%) of vascular events: Allocated antiplatelet	Adjusted control	Observed-expected	Variance
Peripheral arterial disease:					
Intermittent claudication	26	201/3123 (6.4)	249/3140 (7.9)	-22.3	86.6

Are National Cardiac Guidelines being Applied by Vascular Surgeons?

K. Cassar,[1] J. J. F. Belch[2] and J. Brittenden[1]*

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Introduction. National cardiac guidelines recommend that patients with intermittent claudication should be managed in the same way as those with established coronary heart disease. This survey aimed to determine the attitudes of vascular consultants to risk factor management in new patients attending their out-patient clinic.
Methods. An anonymous postal questionnaire was sent to all 394 members of the Vascular Surgical Society in June 2002. Questions were asked about the following measures: serum cholesterol levels, the presence of diabetes, antiplatelet therapy, exercise regimens, blood pressure, thrombophilia, smoking and the availability of local guidelines and expertise.
Results. A response rate of 65% was obtained. Most (85%) consultants would measure a random cholesterol, but 34% would only treat claudicants if the cholesterol was greater than 5.5 mmol/l. Furthermore, 23% would inappropriately use diet alone as initial cholesterol lowering therapy. Over a quarter of consultants would not screen for diabetes or measure blood pressure. Nearly all (99%) would recommend aspirin and 66% would recommend nicotine replacement therapy. Only 58% had access to a smoking cessation clinic, and 34% to a formal exercise program. The majority (56%) did not have local risk factor management guidelines, only 16% had access to a vascular physician, and 65% would prefer to have this expertise available for difficult cases.
Discussion. Management of major risk factors was found to be sub-optimal. Thus guidelines for the prevention of coronary disease in clinical practice are not being applied to claudicants.

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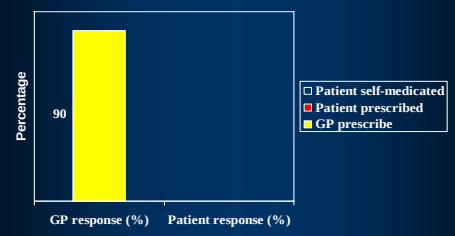
Management of secondary risk factors in patients with intermittent claudication

K Cassar, R Coull, P Bachoo, E Macaulay, J Brittenden
European Journal of Vascular and Endovasc Surgery 26:262-66 (2003)



Management of secondary risk factors in patients with intermittent claudication

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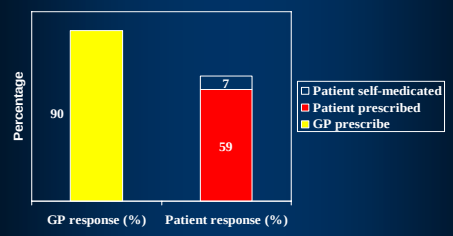
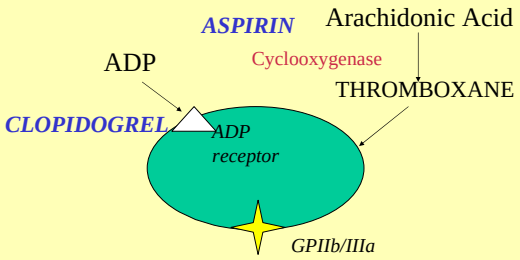


Antiplatelet Drugs



Clopidogrel

Subgroup and treatment group	Individual first-outcome events				Other vascular death	Total	Event rate per year	Relative risk reduction (95% CI)	p
	Stroke		MI						
	Non-fatal	Fatal	Non-fatal	Fatal					
Stroke									
Clopidogrel (nyrs=6054*)	298	17	33	11	74	433	7·15%	7·3% (−5·7 to 18·7)	0·26
Aspirin (nyrs=5979)	322	16	37	14	72	461	7·71%		
MI									
Clopidogrel (nyrs=5787)	37	5	143	20	86	291	5·03%	−3·7% (−22·1 to 12·0)	0·66
Aspirin (nyrs=5843)	34	8	152	22	67	283	4·84%		
PAD									
Clopidogrel (nyrs=5795)	70	11	50	18	66	215	3·71%	23·8% (8·9 to 36·2)	0·0028
Aspirin (nyrs=5797)	74	8	81	27	87	277	4·86%		
All patients									
Clopidogrel (nyrs=17636)	405	33	226	49	226	939	5·32%	8·7% (0·3 to 16·5)	0·043
Aspirin (nyrs=17519)	430	32	270	63	226	1021	5·83%		

*Patient years at risk. MI=myocardial infarction; PAD=peripheral arterial disease.

The CAVA Study

A randomised, double-blind, placebo controlled trial of clopidogrel and aspirin versus aspirin alone in patients undergoing endovascular intervention for claudication

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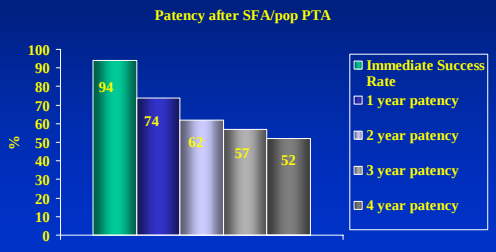
Departments of Medicine and Therapeutics, and Vascular Surgery, University of Aberdeen; Vascular Unit, Aberdeen Royal Infirmary

Restenosis and reocclusion



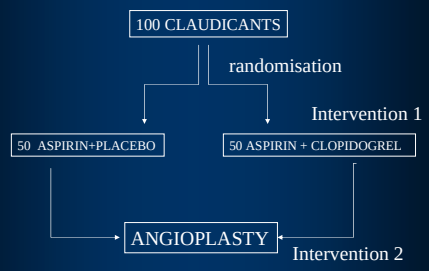
Karch LA et al. J Vasc Surg 2000; 31:880-7

Hypothesis

- In patients undergoing PTA/stenting clopidogrel and aspirin in combination reduce platelet activation and platelet responsiveness more effectively than aspirin alone
- Power calculation: 100 patients $p<0.05$, $\alpha=0.8$

(Moshfegh et al; 2000 J Am Coll Card 36:699-705)

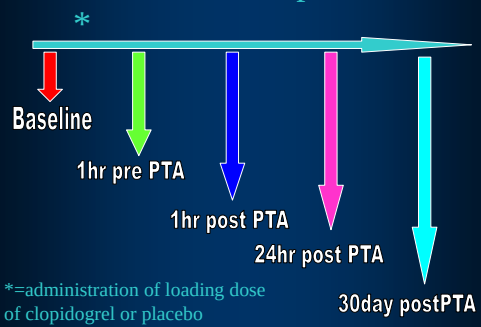
STUDY DESIGN
(double blind RCT)



Outcome measures

- Primary
  - Platelet activation
    - Platelet P-selectin expression
    - Platelet fibrinogen binding
  - Platelet responsiveness to stimulation
    - ADP-stimulated platelet fibrinogen binding

Blood Samples

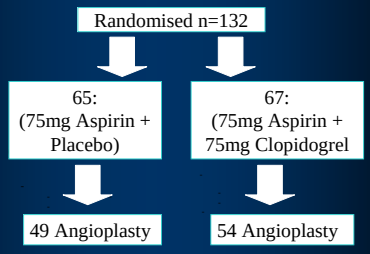


*=administration of loading dose of clopidogrel or placebo

Statistical Analysis

- SPSS Version 10.1
- ANOVA:mixed factorial
- P<0.05 statistically significant
- Chi-squared test/Fisher's exact test: differences in adverse events between the two groups

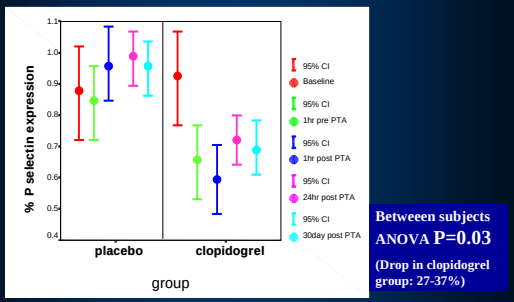
Results: flow of participants



No patients were lost to follow-up

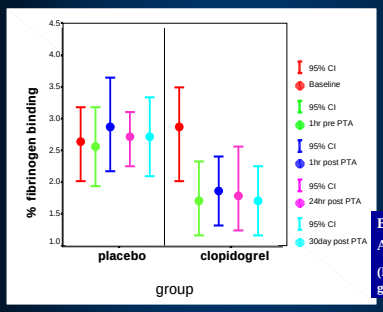
Characteristic	Placebo (n=65)	Clopidogrel (n=67)
Males:females	50:15	52:15
Mean Age/years (Range)	65.4 (46-80)	66.1 (43-80)
Smoking (%)		
never	3 (4.6)	5 (7.5)
ex-smoker > 1year	27 (41.5)	28 (41.8)
ex-smoker < 1 year	13 (20.0)	11 (16.4)
smoker	22 (33.8)	23 (34.3)
Diabetes (%)	11 (16.9)	12 (17.9)
Mean Serum cholesterol mmol/L (STD)	3.68 (2.23)	4.15 (2.02)
Ankle Brachial Pressure Index	0.63	0.65

P-selectin expression



Betweeen subjects ANOVA P=0.03
(Drop in clopidogrel group: 27-37%)

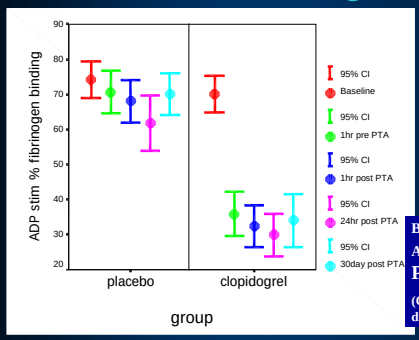
% Fibrinogen binding



Betweeen subjects ANOVA P=0.026

(Drop in clopidogrel group: 31-40%)

ADP-stimulated fibrinogen binding



Between subjects ANOVA: P<0.001

(Clopidogrel group: drop 49-57%)

Adverse Events

- No difference in bleeding complications
- No patients required surgical intervention for bleeding

Results

- Clopidogrel-aspirin combination compared to aspirin alone significantly reduces:
  - platelet activation and
  - platelet responsiveness to stimulation

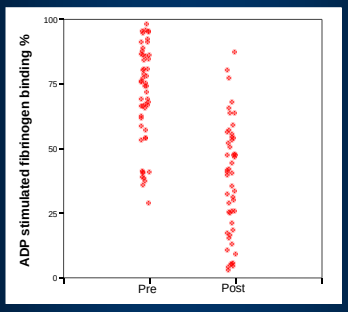
Conclusion

- The combination of aspirin-clopidogrel may:
  - reduce the risk of cardiovascular events
  - reduce the incidence of restenosis and reocclusion after peripheral angioplasty in claudicants
- Need for Randomised controlled trials with clinical outcome measures

Is the antiplatelet drug having an antiplatelet effect in this patient?

Aspirin Resistance

Clopidogrel resistance??



Future research

- Development of reliable simple point-of-care test of platelet function:
  - To allow correlation between platelet activation and risk of vascular events
  - to guide use of antiplatelet treatment