Should Bivalirudin Replace UFH during Peripheral Intervention? APPROVE and other experiences

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Disclosure Information

- ✓ Research / Grant Support:

  Cordis, Guidant, BSC, Medtronic, Edwards, Eli Lilly, The Medicines Co.

- ✓ Consultation:

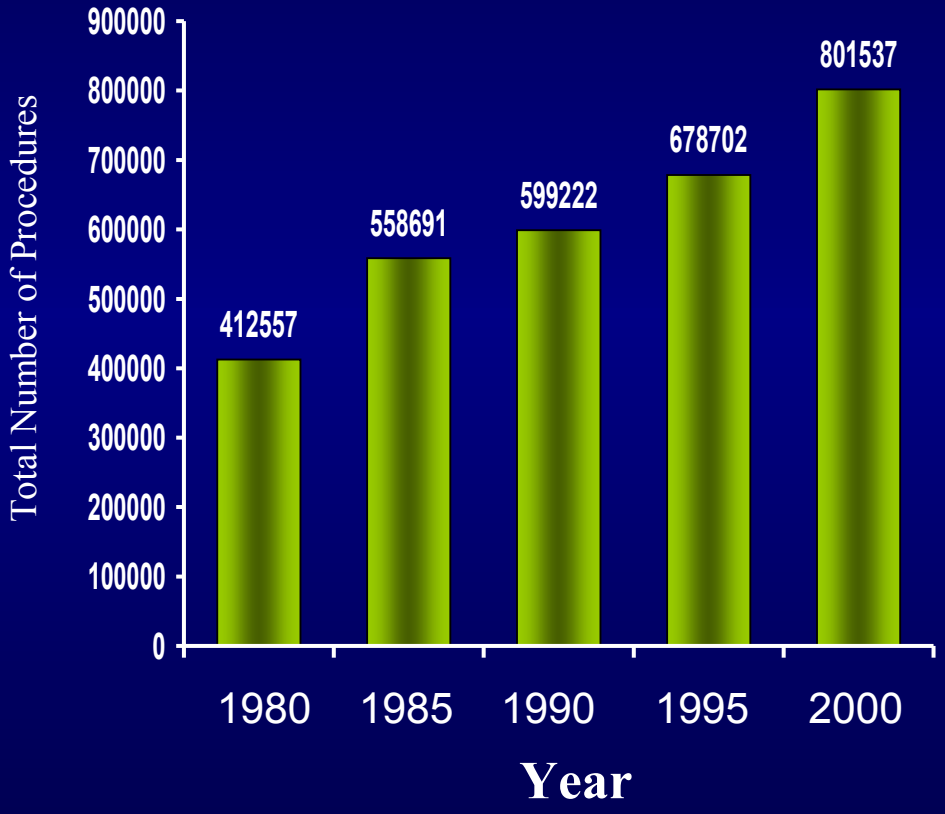
  Cordis, Guidant

- ✓ Speakers Bureau:

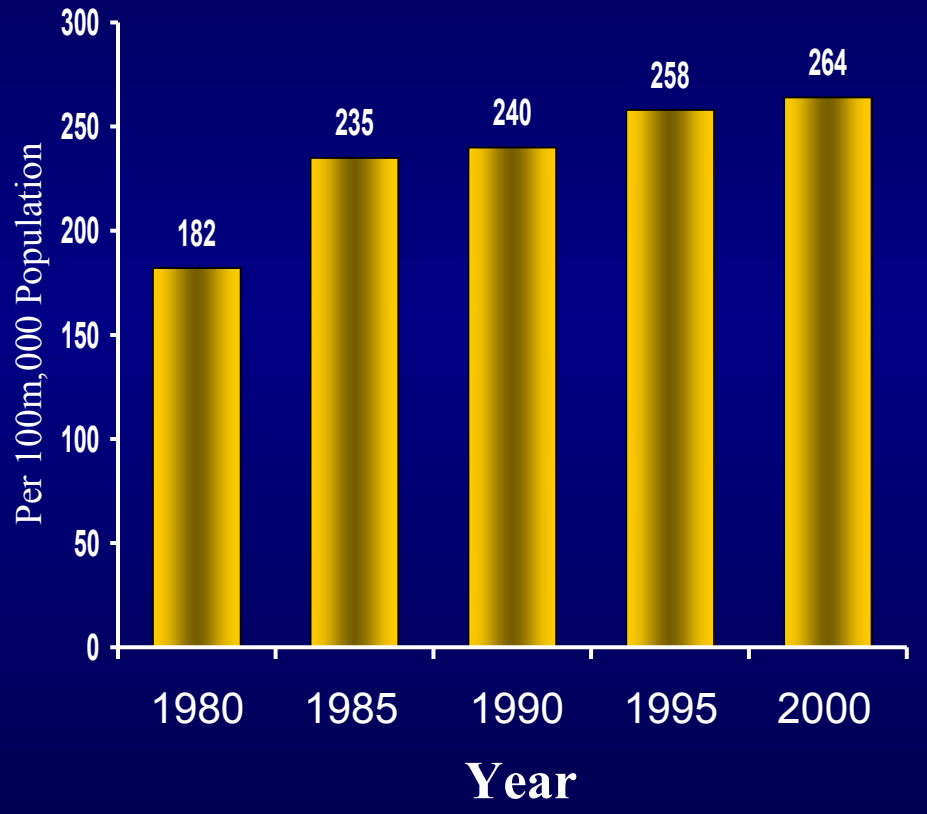
  Cordis, Guidant, Eli Lilly, BMS, Sanofi

Trends in Vascular Intervention

Growth in Total Number of Vascular Procedures from 1980 to 2000



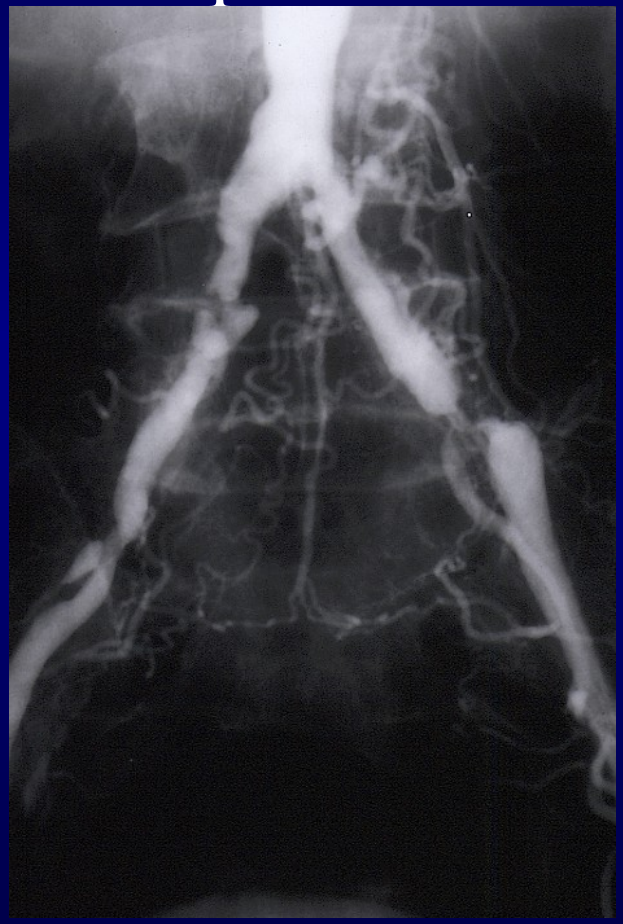
Growth in Per Capita Rate for All Vascular Procedures from 1980 to 2000



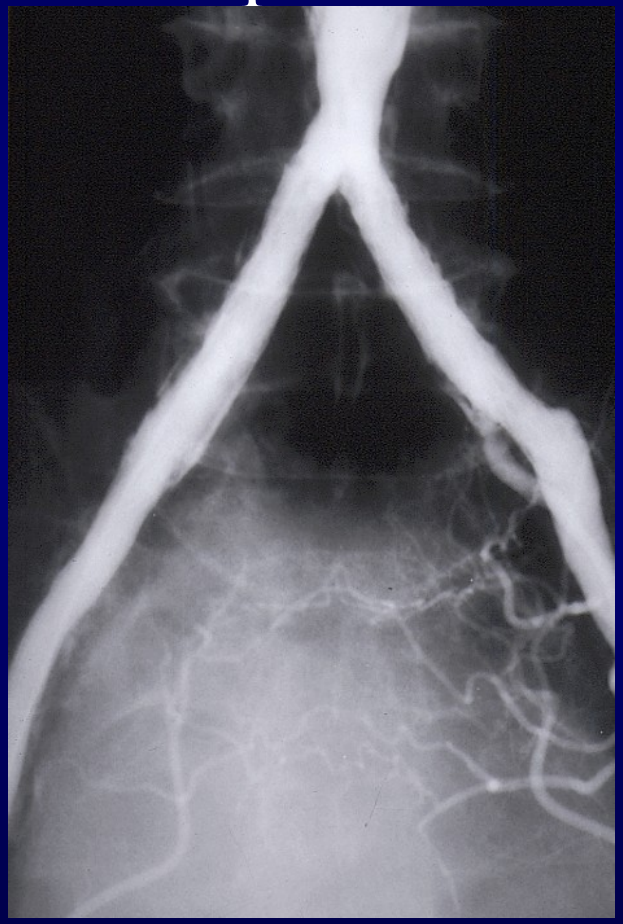
Anderson PL, et al. J Vascular Surg 2004;39:1200-8

Aorto-Iliac Stent Results

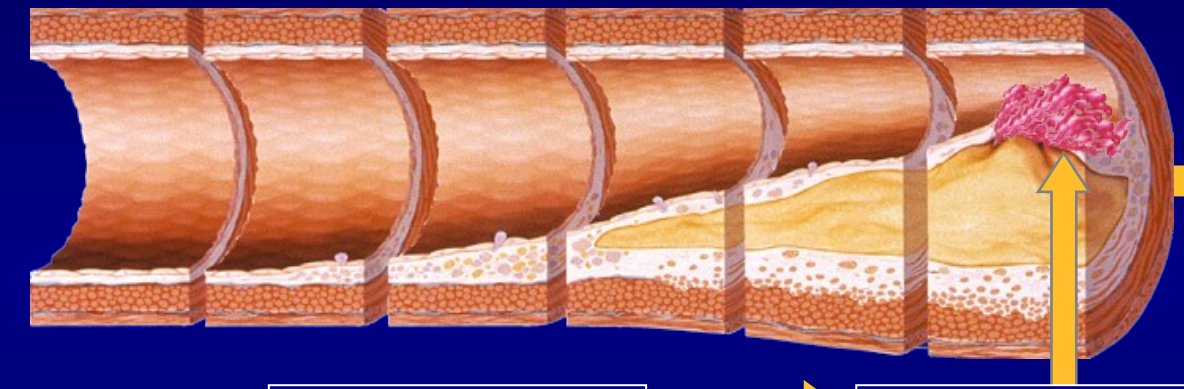
- Pre-procedure



- Post-procedure



Atherothrombosis: A Generalized and Progressive Process



Atherosclerosis

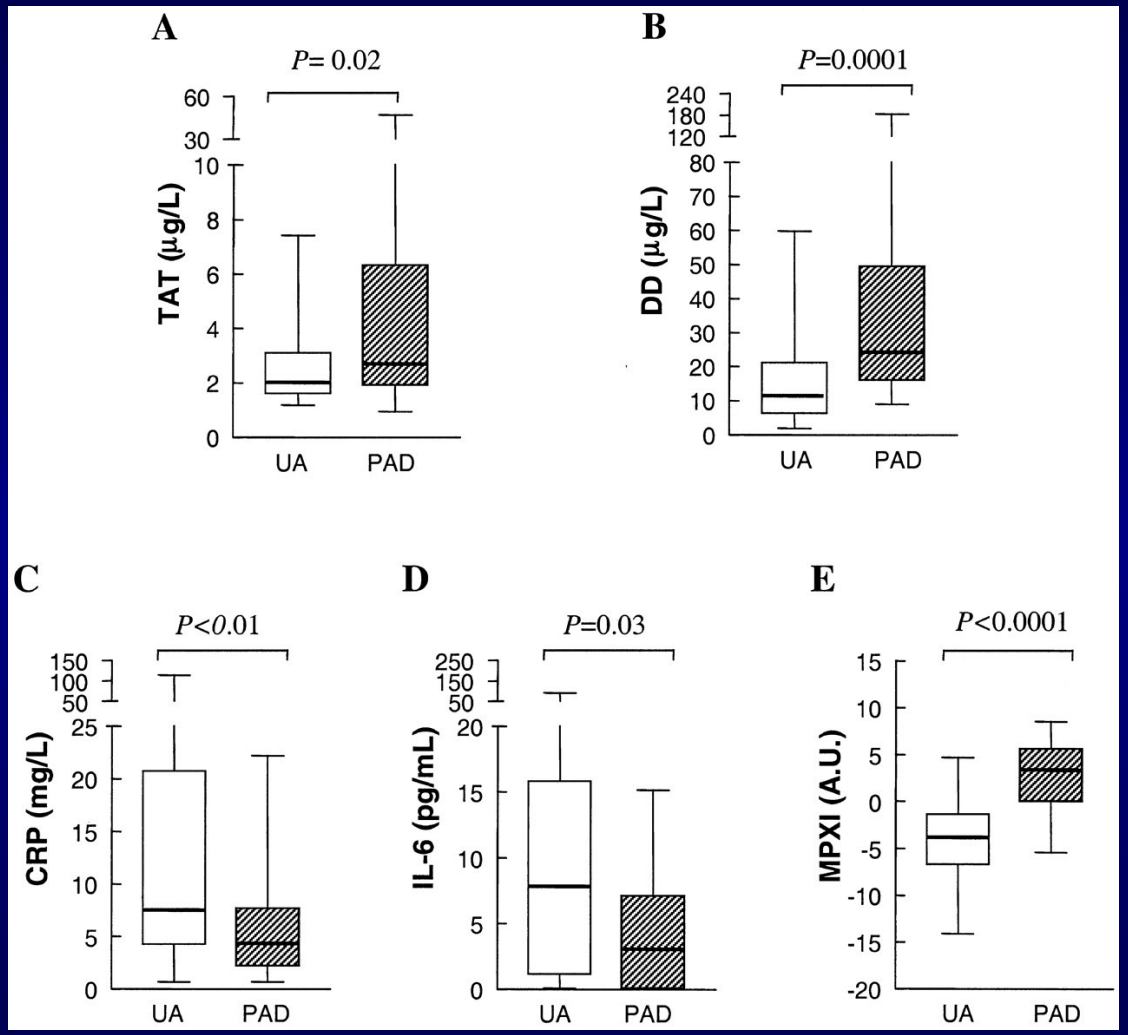
Atherothrombosis

- Unstable Angina
- MI
- Ischemic Stroke/TIA
- Critical Leg Ischemia
- Cardiovascular Death

Stable Angina
Intermittent Claudication

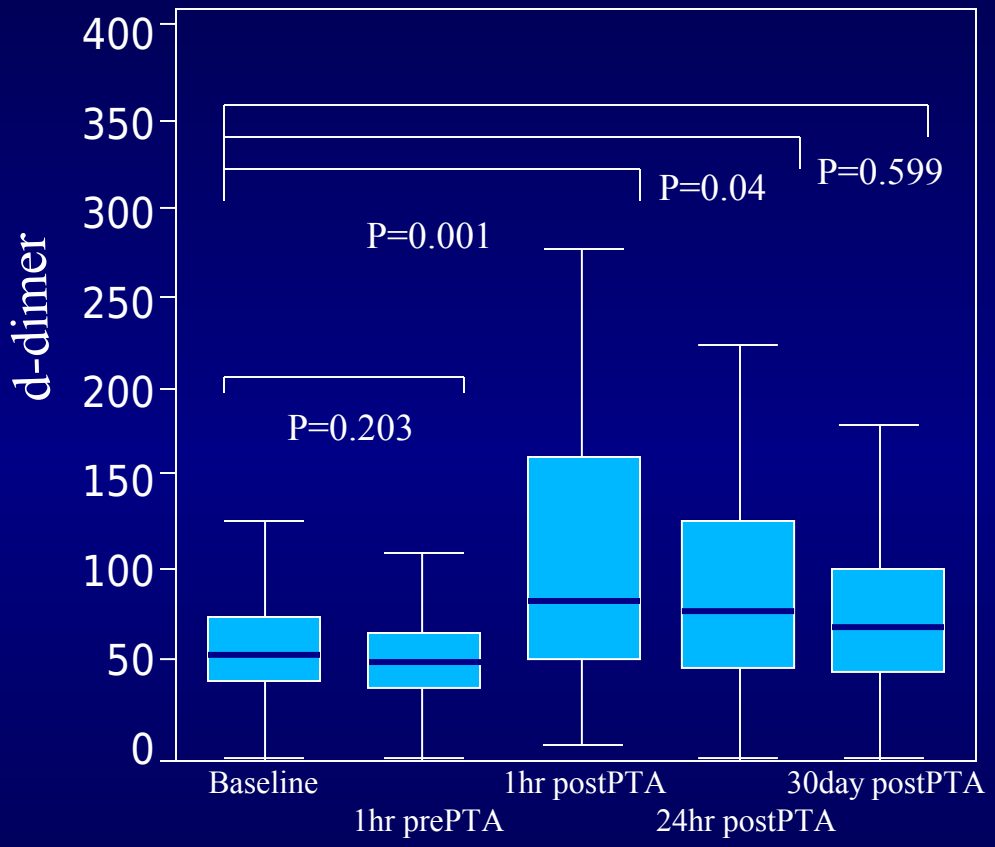
Adapted from Fuster V, et al. *Vasc Med*. 1998;3:231-239
and Stary HC, et al. *Circulation*. 1995;92:1355-1374.

Activation of the Coagulation Cascade and Circulating Inflammatory Markers in UA (open boxes) and PAD (shaded boxes)

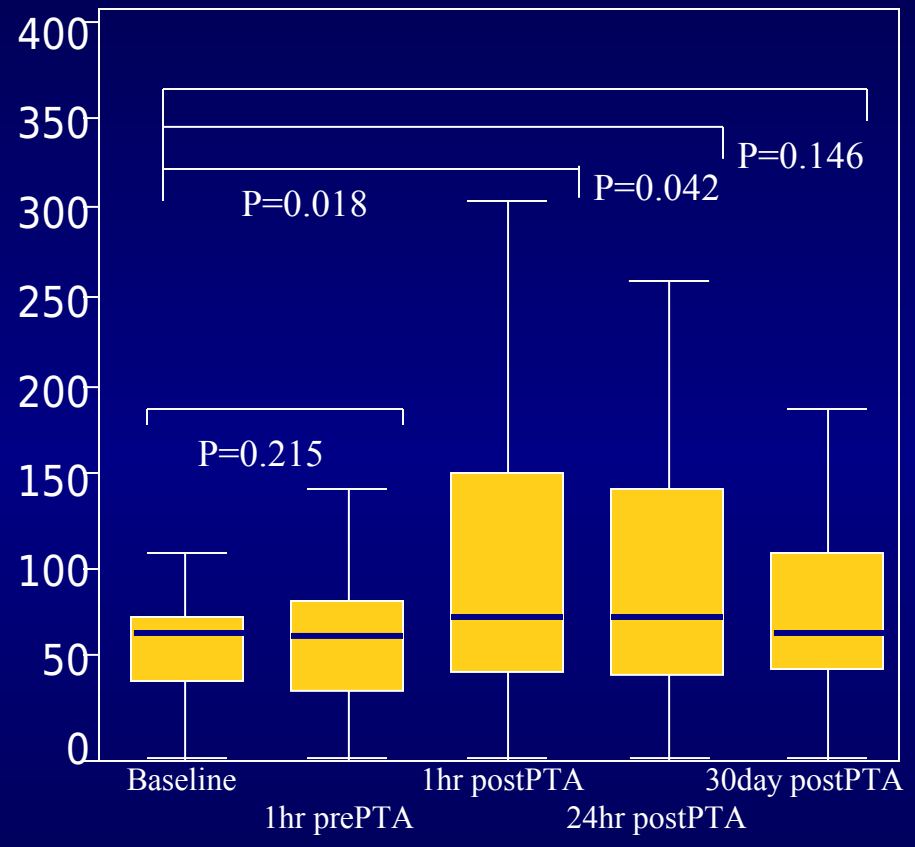


Monaco, C. et al. J Am Coll Cardiol 2005;45:238-243

D-dimer Levels during Peripheral Intervention Placebo and Clopidogrel Groups Over Time



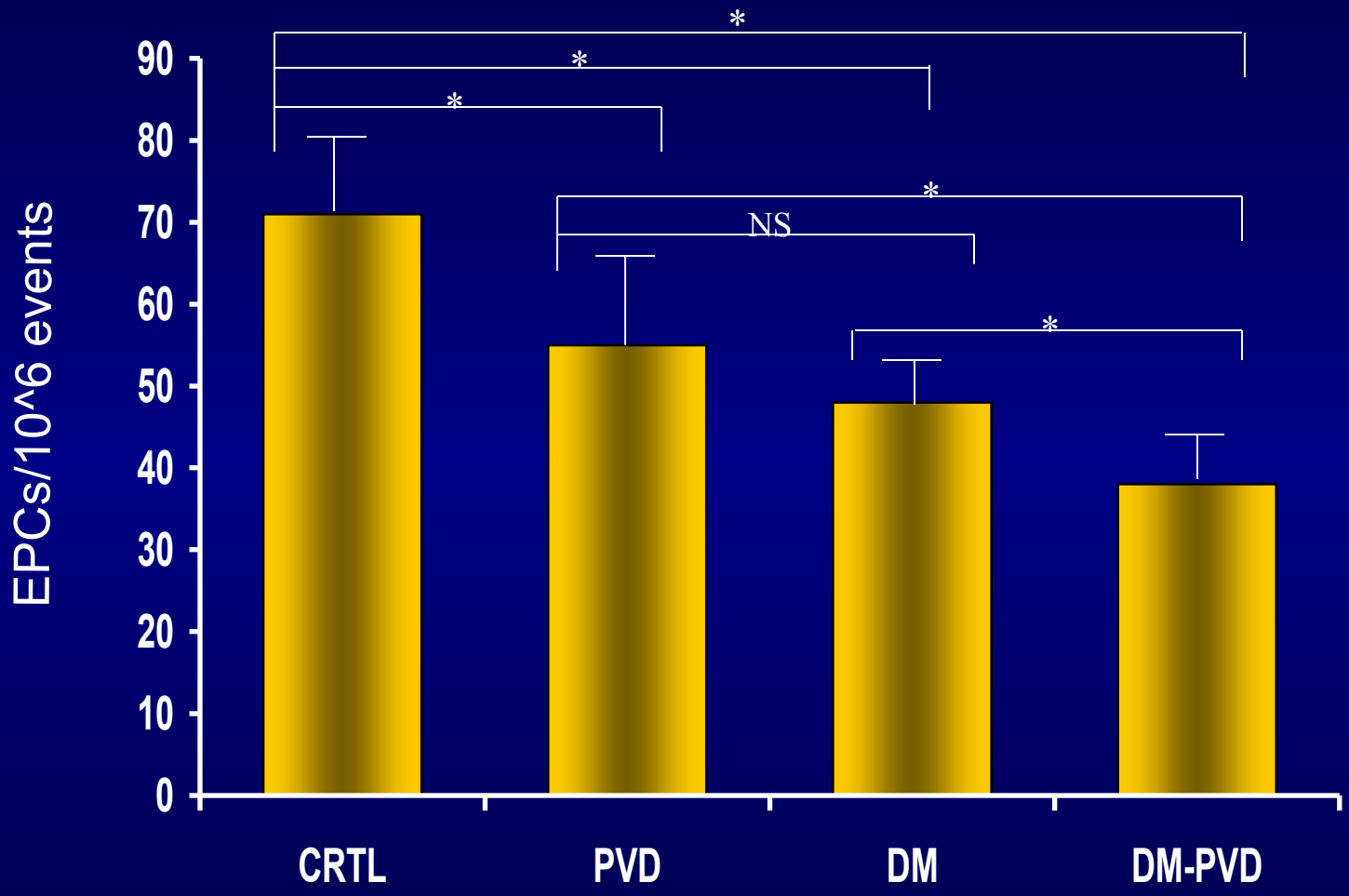
Placebo



Clopidogrel

Cassar K et al. J Vasc Surg. 2005;42:252-8.

Circulating endothelial progenitor cells (EPCs) in PAD and DM



*p<0.05

Fadini, G. P. et al. J Am Coll Cardiol 2005;45:1449-1457

Percutaneous Peripheral Interventions (PPI)

- Thrombus occurs in 100% of cases
- Bleeding risks are higher (diseased vessel, larger sheaths, longer procedure times)
- "Low flow" state versus coronary flow
- ↑ incidence of CRI
- ↑ incidence of DM
- PAD pts are hypercoaguable

Overcoming limitations of heparins

Attribute	UFH	LMWH	Bivalirudin
Active moieties in substance	30-35%	15-20%	100%
Action independent of AT	No	No	Yes
Inhibits fibrin-bound thrombin	No	No	Yes
Platelet activation/aggregation	Yes	+/-	Inhibits
PF-4 complexing & risk of HIT	Yes	Reduced	No
Non-specific protease binding	Yes	Partial	No
Variable PK-PD	Yes	Less	No
$T_{0.5}$ in minutes	60-90’	270’	25’

Bivalirudin in PPI

Single Center studies	St Joseph's Hospital Registry
	Naples Endovascular
	Cardiovascular Research Foundation & Lenox Hill
	Genesis Heart Institute
	Cardiovascular Inst of the South
	Baptist Cardiac & Vasc Inst

Direct Thrombin Inhibition in PVD

APPROVE

Angiomax Peripheral Procedure Registry of Vascular Events

Principal Investigators:

David Allie MD Cardiovascular Institute of the South
Patrick Hall MD South Carolina Heart Center

Allie D et al, J Invas Cardiol. 2004;16:651-656

Site Participation

Ohio Heart Health Center	51	Midwest Heart Foundation	18
Washington Hospital Center	46	Washington Adventist Hospital	17
Winchester Medical Center	38	The Heart Center of Indiana	16
Genesis Health System	35	Arizona Heart Hospital	16
Cardiovascular Institute of the South	31	St Luke's Medical Center, WI	12
Miami Heart Institute	26	University of Chicago Hospitals	10
Midwest Cardiology Research	24	Cleveland Clinic Foundation	10
Swedish Medical Center	23	Stanford University Hospital	10
St John's Hospital, Springfield	23	Beth Israel Deaconess	08
South Carolina Heart Center	21	Watson Clinic	05
William Beaumont Hospital	19	Charleston Area Medical Center	04
St Elizabeth's Medical Center	18	Duke University Medical Center	03
Baptist Memorial Hospital	18	St Mary's Medical Center, MI	02

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Angiomax Peripheral Procedure Registry of Vascular Events

Study Objective and Design

- To demonstrate that bivalirudin can safely replace UFH as the primary anticoagulant in patients undergoing PPI, including outpatient (<23hour)
- Open label trial of bivalirudin anticoagulation in renal, femoral, and iliac interventions
- 505 patients / 26 sites
- Bivalirudin 0.75 mg/kg IV bolus + 1.75 mg/kg/hr IV infusion for duration of procedure
- GP IIb/IIIa's / post-procedure bivalirudin → operators discretion

Allie D et al, J Invas Cardiol. 2004;16:651-656

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Angiomax Peripheral Procedure Registry of Vascular Events

Endpoints

- ***Primary:*** **Procedural success defined as ≤ 20% residual stenosis as determined by the treating physician.**
- ***Secondary:***
  - **Activated clotting times (ACTs)**
  - **Health economics (time to sheath removal, ambulation, discharge, use of closure devices)**
  - **Death, MI**
  - **Unplanned revasc or surgical intervention for ischemia (including amputation)**
  - **Bleeding complications**
  - **Renal function (relation to ischemic and bleeding outcomes)**

Allie D et al, J Invas Cardiol. 2004;16:651-656

Patient demographics

Characteristic		
Age (mean)		69
Age > 65 yrs n/N (%)	320/505	(63.4)
Age > 75 yrs n/N (%)	164/505	(32.5)
Female n (%)	231	(45.7)
Male n (%)	274	(54.3)
Angina History n/N (%)	178/504	(35.3)
Prior MI n/N (%)	124/505	(24.6)
Prior Vascular Surgery n/N (%)	175/505	(34.7)
Current Smoker (<6 mos) n/N (%)	152/505	(30.1)
Hyperlipidemia n/N (%)	400/505	(79.2)
Hypertension n/N (%)	450/504	(89.3)
Congestive Heart Failure n/N (%)	79/505	(15.6)
Diabetes (insulin-dependent) n/N (%)	63/505	(12.5)
Diabetes (non insulin-dependent) n/N (%)	120/505	(23.8)

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Primary lesion/vessel

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Renal	**n/N (%)**	**173/505 (34.3)**
Iliac	**n/N (%)**	**140/505 (27.7)**
Femoral	**n/N (%)**	**184/505 (36.4)**
Other*	**n/N (%)**	**8/505 (1.6)**

**** Other arteries include subclavian(2), popliteal(2), tibial(2), tibioperoneal(1), peroneal(1).***

- Clopidogrel pretreatment (300mg) 95.0%
- Aspirin pretreatment (325 mg) 96.8%
- GP IIb/IIIa inhibitors 4.4%

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Activated Clotting Time

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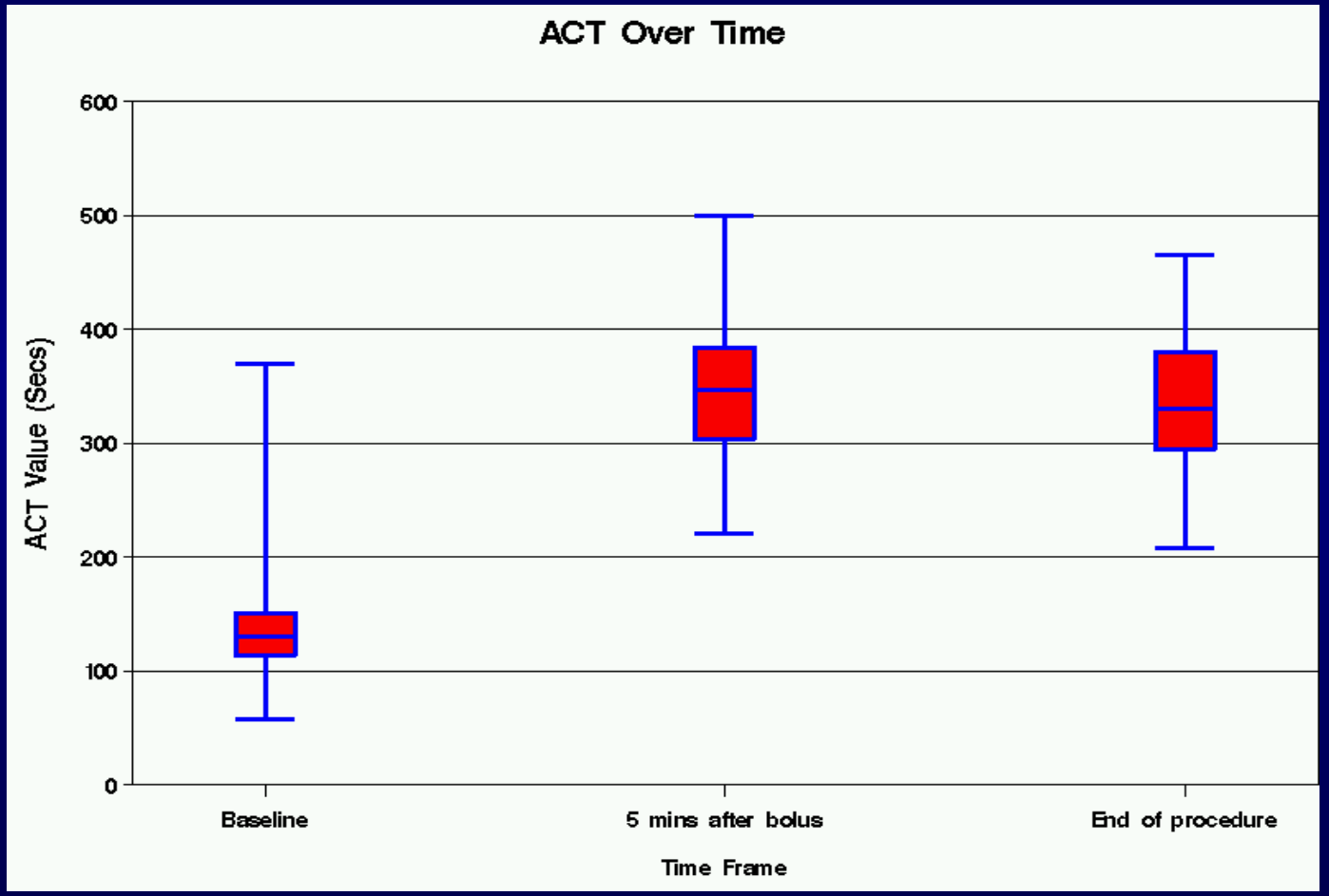
Demonstrating consistent anticoagulation at the dose tested



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Hemorrhagic outcomes: Discharge

	Renal	Iliac	Femoral	Total
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Major (protocol)	4/173 (2.3)	4/140 (2.9)	3/184 (1.6)	11/505 (2.2)
Tx ≥2 U	**2/173 (1.2)**	**4/140 (2.9)**	**1/184 (0.5)**	**7/505 (1.4)**
Intracranial	**0/173 (0.0)**	**0/140 (0.0)**	**0/184 (0.0)**	**0/504 (0.0)**
Retroperitoneal	**0/173 (0.0)**	**1/140 (0.7)**	**1/184 (0.5)**	**2/504 (0.4)**
Fall in Hgb >4g/dL w/no site	**0/173 (0.0)**	**3/140 (2.1)**	**2/184 (1.1)**	**5/505 (1.0)**
Fall in Hgb >3g/dL overt	**2/173 (1.2)**	**0/140 (0.0)**	**1/184 (0.5)**	**3/504 (0.6)**
Minor (protocol)	10/173 (5.8)	14/140(10.0)	19/184 (10.3)	43/504 (8.5)
Major (TIMI)	0/169 (0.0)	1/138 (0.7)	1/179 (0.6)	2/494 (0.4)
Minor (TIMI)	2/173 (1.2)	4/140 (2.9)	4/184 (2.2)	10/505 (2.0)

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Outcomes: 30 days

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	Renal N=173 n (%)	Iliac N=139 n (%)	Femoral N=184 n (%)	Total N=504 n (%)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unplanned revasc	0 (0.0)	0 (0.0)	4 (2.2)	4 (0.8)
Amputation	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.4)
MI	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
New Q- wave*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CK-MB>3XULN	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Major Bleed (prot)	7/173 (4.0)	5/140 (3.6)	7/184 (3.8)	19/505 (3.8)
Minor (protocol)	13/173 (7.5)	14/139(10.1)	21/184 (11.4)	48/504 (9.5)
Major (TIMI)	1/168 (0.6)	1/137 (0.7)	4/177 (2.3)	6/490 (1.2)
Minor (TIMI)	4/172 (2.3)	4/139 (2.9)	7/181 (3.9)	15/500 (3.0)

•*New Q-wave >0.04 sec duration in 2 or more contiguous leads

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Renal Function

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	Creatinine Clearance* (mL/min)			
	<30 N=32 n (%)	30-59 N=187 n (%)	60-89 N=164 n (%)	> 90 N=120 n(%)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unplanned revasc	0 (0.0)	1 (0.5)	2 (1.2)	1 (0.8)
Amputation	0 (0.0)	1 (0.5)	1 (0.6)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Bleeding at Discharge				
Major (protocol)	1 (3.1)	4 (2.1)	4 (2.4)	2 (1.7)
Major (TIMI)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)

* Measured at baseline

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Summary:
APPROVE 30-day outcomes

- Bivalirudin, as the sole procedural anticoagulant, provided similar outcomes in all vessel types treated
- Consistent anticoagulation at the dose tested
- No deaths, incidence of hemorrhagic complications & amputation were low
- Times to sheath removal (2.67 h), ambulation (8.78 h), and discharge (20.9 h) were favorable and may allow same-day discharge without compromising efficacy or safety
- Support conclusion that bivalirudin provides safe and reliable anticoagulation in patients undergoing PPI

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Bivalirudin in Carotid Intervention

Single Center experience	Lenox Hill Heart & Vascular Institute
	North Shore University Hospital
	Wake Med
	Baylor and DeBakey VA

Baylor and DeBakey carotid experience

	Group I Case 1-50 N=50 (%)	Group II Case 51-100 N=50 (%)	Group III Case 101-150 N=50 (%)	Group IV Case 151-200 N=50 (%)
Tech success	47 (94%)	49 (98%)	50 (100%)*	50 (100%)*
Length of stay (d)	1.6 ± 1.3	1.3 ± 1.1	1.4 ± 0.7	1.5 ± 0.6
Procedural time (m)	58 ± 10	43 ± 11*	39 ± 8**	36 ± 10**
Contrast used	98 ± 24	79 ± 19*	55 ± 15**	53 ± 12**

* p< 0.05 compared with Group I
** p <0.03 compared with Group I

Lin PH et al, *Pers Vasc Surg Endovasc Ther.* 2005;17:113-125

Baylor and DeBakey carotid experience

	Group I Case 1-50 N=50 (%)	Group II Case 51-100 N=50 (%)	Group III Case 101-150 N=50 (%)	Group IV Case 151-200 N=50 (%)
Complications				
Cardiopulmonary	2(4%)	2(4%)	1(2%)	1(2%)
Hemorrhagic	3(6%)	1(2%)	0*	0*
Stroke (TIA)	1(2%)	0	0	0
Stroke (minor)	1(2%)	1(2%)	0	0
Stroke (major)	1(2%)	0	0	0
30-day death	1(2%)	0	0	0
30-day stroke/death	4 (8%)	1(2%)*	0**	0**
Overall complication	9 (18%)	4 (8%)**	1(2%)***	1(2%)***

* p< 0.05 compared with Group I
** p <0.03 compared with Group I
***p <0.01 compared with Group I

Lin PH et al, *Pers Vasc Surg Endovasc Ther.* 2005;17:113-125

Bivalirudin Use During Peripheral Intervention - Conclusion

- Safe alternative to UFH
- Predictable anticoagulation during PPI
- Adverse ischemic events are low
- Bleeding rates less than UFH
- Decreased sheath removal & ambulation times
- Ongoing studies
  - COBRA: carotid study
  - Use with GP IIb/IIIa inhibitors (CLI / high risk pts)