UNIVERSITÉ PARIS DESCARTES

AMÉLIORER L'IMPACT PHARMACO-ÉCONOMIQUE DE SA PRATIQUE

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DISCLOSURES

- Research grants:
  - The Medicines Company, TERUMO, MSD-Schering
- Fees for giving lectures and/or consulting:
  - MSD-Schering, Servier, The Medicines Company, ART

Contexte

- Pour les médecins, l'objectif principal est de proposer aux patients le traitement ayant le meilleur rapport entre le risque et le bénéfice.

Rappels et généralités concernant l'analyse médico-économique

INTRODUCTION (1)

- L'évaluation médico-économique fait partie des variables qui permettent de faire un choix et/ou de prendre une décision.

- La pharmaco économie (focalisée sur le prix des médicaments) est une branche de la médico économie. Toute action de santé doit être évaluée afin de faire le **meilleur choix** pour le patient et pour la société.

- **Ce choix est considéré comme nécessaire** car les soins et la santé ont des ressources qui sont prélevées sur une grande partie de la société au nom de la solidarité et le budget consacré étant borné, tout choix n'incluant pas un volet économique peut être injuste pour le patient car on ne peut pas tout payer …

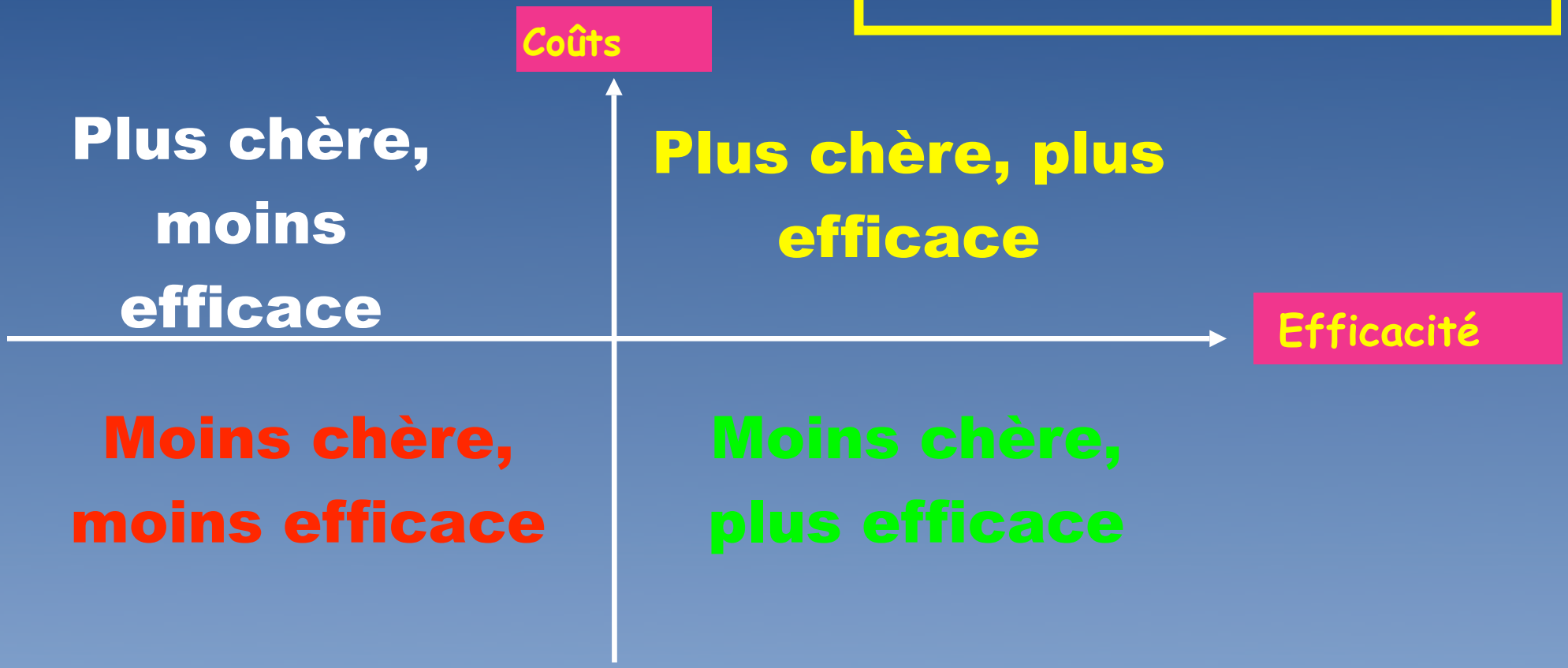
INTRODUCTION (2)

- Finalement l'analyse médico-économique est souhaitable voir indispensable car:
  - Elle apporte un élément supplémentaire dans la décision
  - Elle rend le processus décisionnel plus transparent pour tous les acteurs du système (décideurs, industrie, médecins et les politiques en charge de la politique de santé)

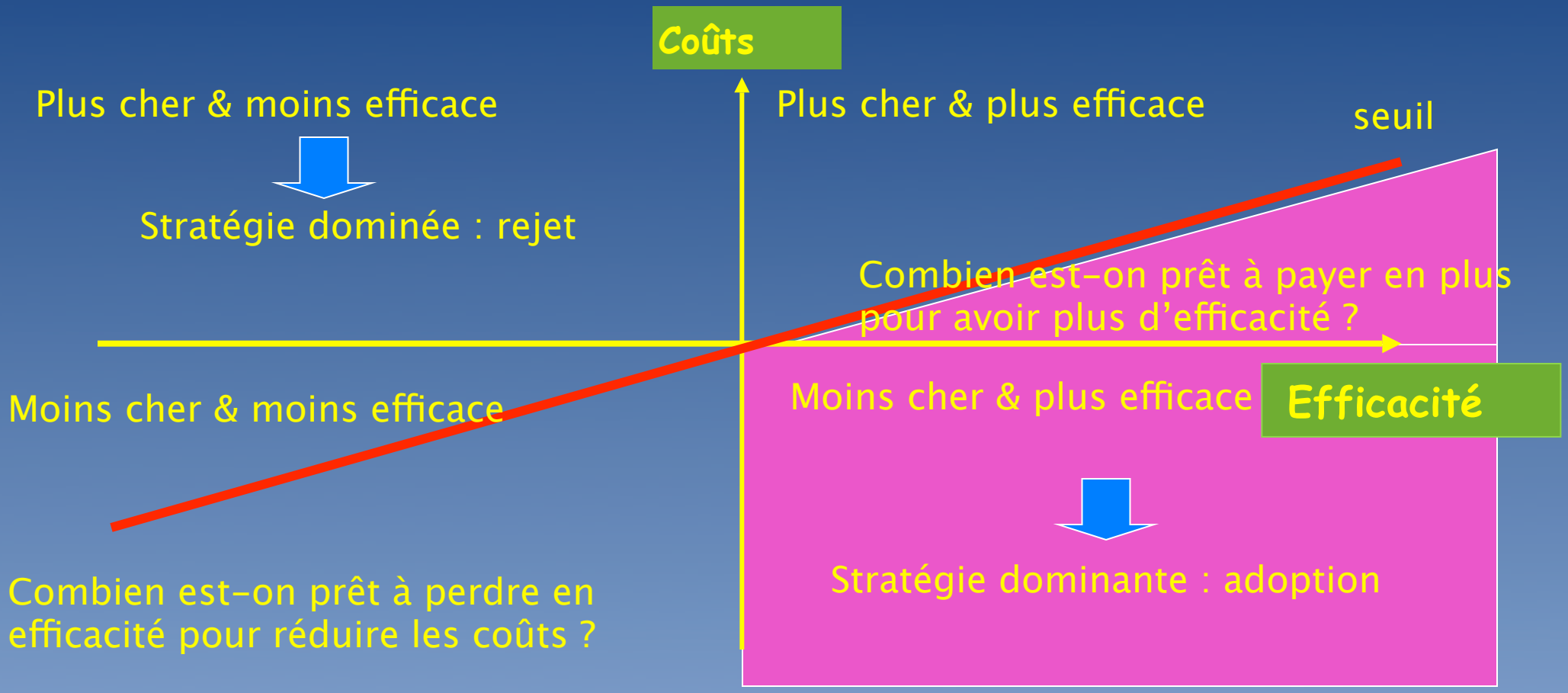
- L'analyse médico-économique peut être réalisée:
  - **Avant la mise sur le marché** afin de connaître son rapport coût/efficacité
  - **Après la mise sur le marché** (Post AMM ou Post marketing) afin de s'assurer que les bénéfices, les risques et les coûts sont bien ceux estimés lors de l'étude pivot avant la mise sur le marché.

Etude Médico-économique: Coût/ Efficacité (CE)

$$CE = \frac{\text{Coût Inov} - \text{Coût usuel}}{\text{Bénef Inov} - \text{Bénef usuel}}$$



Quelle information pour le décideur ?



Approches médico-économiques

1. **Etude ancillaire d'une étude randomisée d'efficacité**
   - ✓ Avantage: deux groupes comparables
   - ✓ Inconvénients: population sélectionnée

   ACUITY (biva vs. UFH/ Enoxaparine), **HORIZONS** (biva vs. UFH/ GPI)

2. **Modélisation à partir de sources multiples**
   - ✓ Avantages: plus près de la vie réelle, possibilité d'analyse de nombreux sous groupes
   - ✓ Inconvénients: nombreux biais de sélection et hypothèses

   Premier registry, and NCDR PCI Bleeding Model

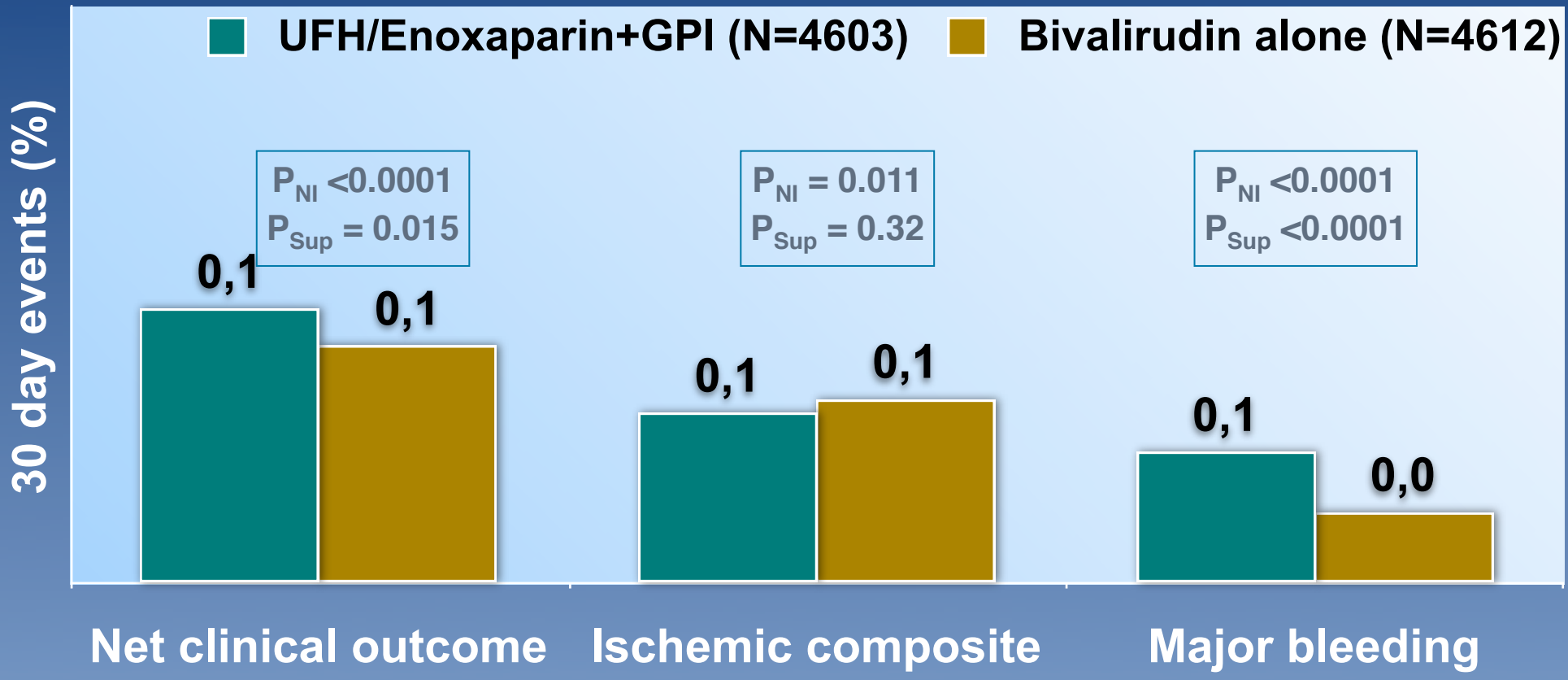
Mesures « Coût/Efficacité »

- **Mesure efficacité:**
  - Quantité de vie
  - Qualité de vie liée à la santé
  - Qalys (Quality adjusted life years saved): quantité de vie ajustée sur la qualité de vie
  - Indicateur plus spécifique (ex: nombre revascularisations évitées, « net clinical outcome » ACUITY)

- **Mesure des coûts:**
  - Directs, indirects (productivité)
  - Coûts initiaux (hospitalier) puis au suivi à un horizon variable (1 mois ACUITY)
  - Coûts réels mesurés: coûts « PMSI » (GHM/GHS)
  - Etudes de sensibilité nécessaires selon les systèmes de soins

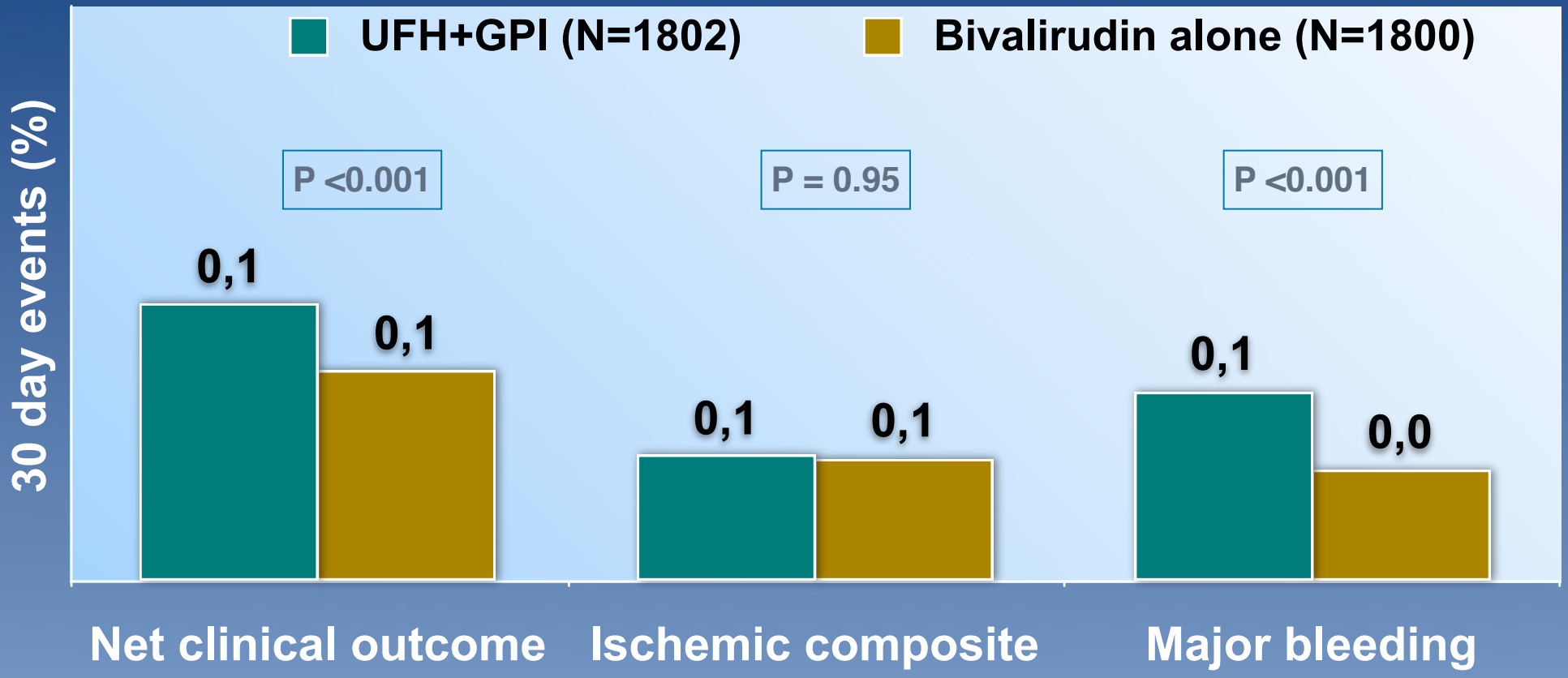
ACUITY: Primary Endpoint Measures (ITT)

UFH/Enoxaparin + GPI vs. Bivalirudin Alone



HORIZONS: Primary Endpoint Measures (ITT)

UFH/Enoxaparin + GPI vs. Bivalirudin Alone



Analyse médico-économique de la bivalirudine aux USA

ACUITY: procedural resource use and costs

Table 2 Procedural Resource Use and Cost

	Heparin		Bivalirudin		Bivalirudin Monotherapy	
	Upstream GPI (n = 1,301)	Catheterization Laboratory GPI (n = 1,308)	Upstream GPI (n = 1,325)	Catheterization Laboratory GPI (n = 1,302)	No GPI (n = 2,615)	p Value
Anticoagulant use, %						
Bivalirudin	2.5	2.0	97.7	97.6	98.8	<0.001
GPI	98.2	53.7	97.7	54.2	7.6	<0.001
LMWH*	42.3	42.5	1.9	2.4	2.7	<0.001
UFH*	62.7	61.5	13.0	11.2	12.8	<0.001
Anticoagulant vials†						
Bivalirudin	1.3 ± 0.6	1.7 ± 1.4	2.0 ± 2.8	2.2 ± 3.9	2.2 ± 2.6	<0.001
Eptifibatide	4.5 ± 2.6	4.6 ± 1.6	4.3 ± 2.4	4.5 ± 1.5	4.7 ± 2.5	<0.001
Tirofiban	1.7 ± 1.7	1.4 ± 0.6	1.6 ± 1.4	1.5 ± 0.6	1.6 ± 1.3	0.90
Abciximab	5.3 ± 1.5	3.8 ± 1.2	3.0 ± 1.4	3.7 ± 0.9	4.1 ± 1.8	0.12
Anticoagulant costs	$896 ± $2,854 [$725]	$515 ± $584 [$399]	$1,537 ± $1,407 [$1,192]	$1,315 ± $1,727 [$1,000]	$976 ± $1,139 [$824]	<0.001
Index PCI resources‡						
Contrast	246 ± 119	248 ± 162	241 ± 120	240.48 ± 120	245 ± 124	0.71
Balloons	1.4 ± 1.3	1.4 ± 1.5	1.4 ± 1.1	1.4 ± 1.2	1.4 ± 1.2	0.86
Number of stents, bare-metal	0.2 ± 0.6	0.2 ± 0.7	0.3 ± 0.7	0.2 ± 0.6	0.3 ± 0.6	0.07
Number of stents, drug-eluting	1.4 ± 1.1	1.3 ± 1.1	1.3 ± 1.1	1.3 ± 1.0	1.4 ± 1.1	0.82
Drug-eluting stent used (%)	83.6	81.0	81.2	81.9	80.7	0.60
PCI costs (excluding anticoagulants)	$5,979 ± $3,058 [$4,888]	$6,009 ± $3,075 [$4,931]	$5,962 ± $2,919 [$4,942]	$5,985 ± $4,323 [$4,823]	$6,058 ± $3,131 [$4,883]	0.98

Pinto et al. JACC

ACUITY: 30-day outcomes and costs

Table 3 Hospital Outcomes, Resource Use, and Costs

	Heparin + GPI		Bivalirudin + GPI		Bivalirudin Monotherapy	
	Upstream GPI	Catheterization Laboratory GPI	Upstream GPI	Catheterization Laboratory GPI	No GPI	p Value
Death, %	0.8	0.3	0.7	0.8	0.9	0.35
MI, %	4.7	4.9	5.1	4.8	5.0	0.99
Unplanned revascularization, %	0.9	0.8	1.1	1.6	0.9	0.22
PCI	0.6	0.5	0.6	1.3	0.7	0.09
CABG	0.3	0.3	0.5	0.3	0.2	0.84
Death or MI, %	5.4	5.0	5.5	5.5	5.6	0.96
Death, MI, or unplanned revascularization, %	5.9	5.6	6.0	6.6	6.0	0.87
Major bleeding, %	5.1	4.3	6.1	3.7	2.7	<0.001
Minor bleeding, %	28.2	20.9	27.5	22.8	14.1	<0.001
Transfusion, %	8.4	7.0	9.1	5.8	6.9	0.007
Length of stay, days	3.7 ± 3.5 [2.0]	3.6 ± 3.4 [2.0]	3.5 ± 3.5 [2.0]	3.3 ± 3.2 [2.0]	3.4 ± 3.3 [2.0]	0.02
ICU length of stay, days	1.3 ± 2.7 [0]	1.2 ± 2.3 [0]	1.2 ± 2.0 [0]	1.2 ± 2.6 [0]	1.2 ± 2.5 [0]	0.10
Costs						
Anticoagulant medications	$896 ± $2,854 [$725]	$515 ± $583 [$399]	$1,537 ± $1,407 [$1,192]	$1,315 ± $1,727 [$1,000]	$976 ± $1,139 [$824]	<0.001
Catheterization laboratory procedures	$3,207 ± $3,775 [$2,672]	$3,243 ± $3,793 [$2,672]	$3,399 ± $3,714 [$3,528]	$3,335 ± $4,435 [$2,887]	$3,336 ± $3,846 [$2,824]	0.58
Hospital room and ancillary services	$8,705 ± $12,301 [$4,757]	$8,610 ± $12,149 [$4,757]	$8,244 ± $11,284 [$4,329]	$7,933 ± $10,139 [$4,329]	$7,887 ± $10,610 [$4,329]	0.04
Physician fees	$2,071 ± $2,620 [$1,486]	$1,957 ± $2,278 [$1,486]	$1,958 ± $2,224 [$1,486]	$1,798 ± $2,115 [$1,430]	$1,867 ± $2,218 [$1,431]	0.02
Total cost for initial hospital stay	$14,416 ± $11,944 [$11,443]	$14,028 ± $12,069 [$11,377]	$14,925 ± $11,652 [$12,058]	$14,153 ± $11,321 [$11,765]	$13,844 ± $11,621 [$10,927]	<0.001
Discharge to 30 days cost	$767 ± $3,254 [$0]	$856 ± $3,370 [$0]	$774 ± $3,230 [$0]	$945 ± $3,691 [$0]	$917 ± $3,610 [$0]	0.658
Total 30-day cost	$15,183 ± $12,646 [$12,018]	$14,884 ± $12,576 [$11,832]	$15,699 ± $12,094 [$12,649]	$15,099 ± $11,991 [$12,304]	$14,761 ± $12,347 [$11,372]	0.005

Heparin + in-lab GPI

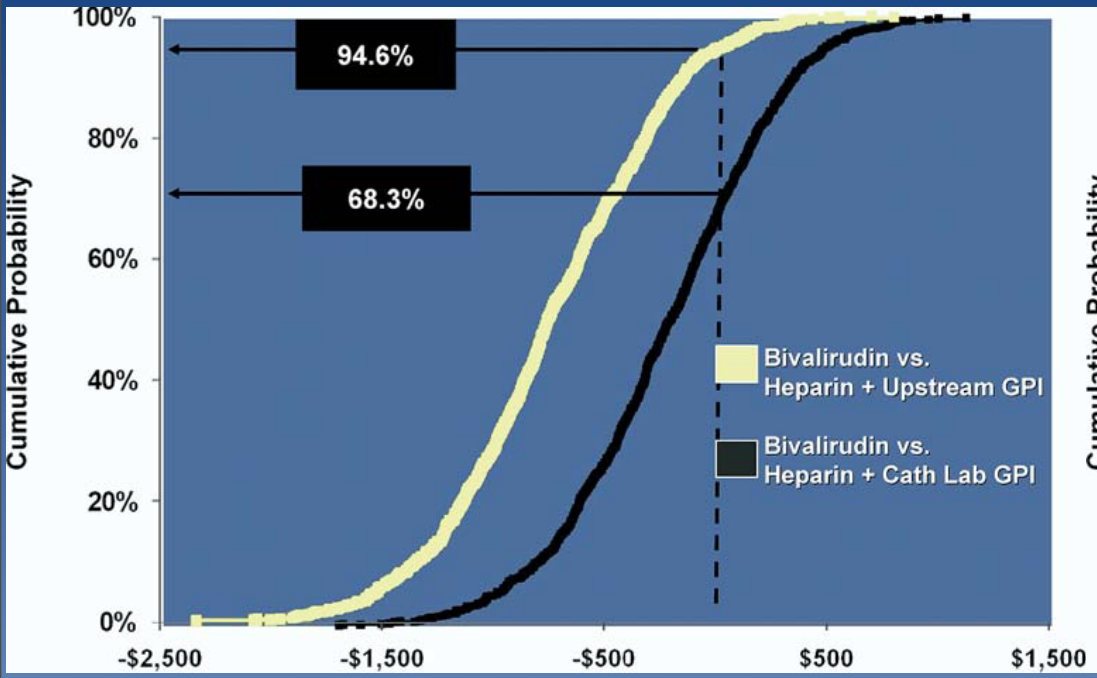
$ 14,884

Bivalirudin alone

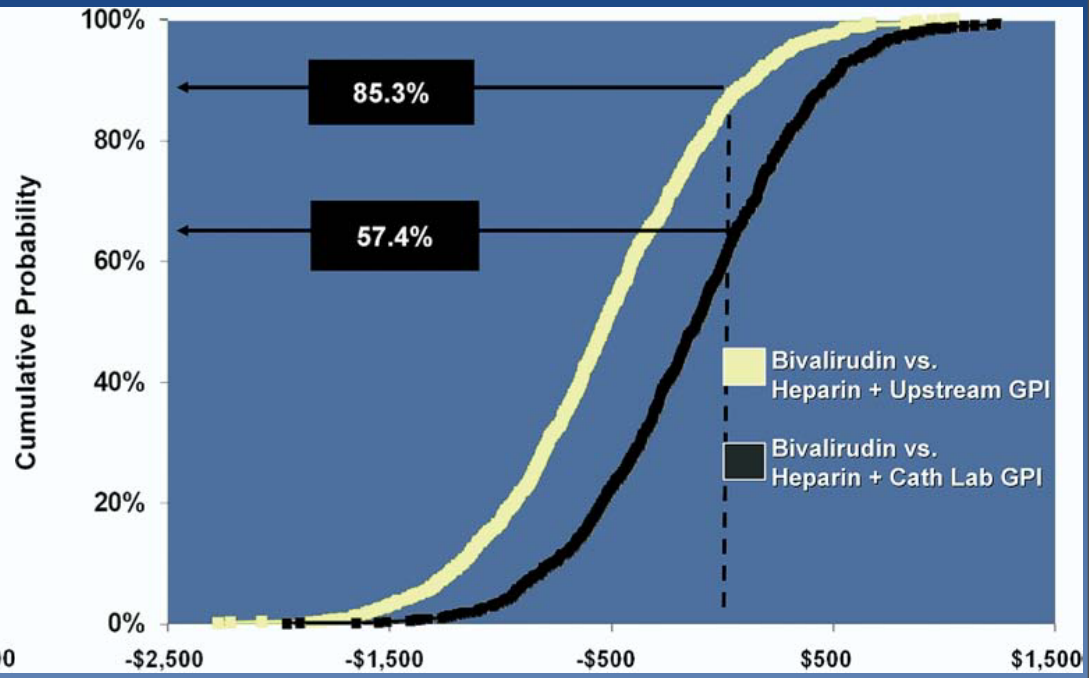
$ 14,761

Pinto et al. JACC

ACUITY: cost-effective analysis



In hospital cost



30-day hospital cost

Regression modeling demonstrated that hospital savings were primarily due to less major and minor bleeding with bivalirudin ($8,658/event and $2,282/event, respectively).

Pinto et al. JACC

PREMIER registry: Economic analysis

- The ability of bivalirudin to reduce bleeding events and preserve low ischemic event rates during PCI has been well documented across the spectrum of stable and ACS patients in randomized controlled trials. Economic analyses from these trials found bivalirudin was associated with reduced hospital costs.
- The economic impact of bivalirudin or heparin use during PCI, with or without GP IIb/IIIa inhibitor (GPI) in unselected patients, is less certain.
- The purpose of this study is to evaluate the impact of anti-thrombin choice on length of hospital stay after PCI (LOS) and cost in a large unselected population.

Bajaj et al, TCT-118 JACC;2010:56(13) Suppl B

Real-world US data (PREMIER database)

2004-2008
452,044 PCI procedures

	BIV (N=155,074	BIV+GPI (N=33,119)	HEP (N=83,999)	HEP+GPI (N=179,852
Age (mean ± SD)	66.1 ± 11.8	63.2 ± 12.0	65.5 ± 12.4	62.5 ± 12.3
Male (%)	63.2	67.3	62.7	68.1
White (%)	75.2	74.5	71.4	73.6
STEMI	5.7	18.7	16.2	30.6
Non-STEMI	12.6	20.2	16.7	20.8
UA	28.7	24.2	24.8	20.8
SA/CIHD	51.6	35.1	40.3	25.8
Other	1.3	1.8	2.0	2.0
Cardiogenic Shock (%)	0.5	1.7	2.1	2.8

Data: Bajaj et al. TCT 2010

Bleeding and costs

	BIV (N=155,074)	BIV+GPI (N=33,119)	HEP (N=83,999)	HEP+GPI (N=179,852
Access-related bleed (%)	1.7	2.8	2.8	3.8
Non-access-related bleed (%)	2.0	3.5	3.0	3.6
LOS post-PCI (days)	0.8 ± 2.5	1.4 ± 3.0	1.5 ± 3.6	1.6 ± 3.2
Cost ($)	13927±10602	17095±12768	15943±13772	16710 ± 11748
Adjusted cost difference ($)	- 1116 ± 39	+ 1320 ± 63	-650 ± 45	Ref

Cost of bivalirudin less than heparin+GPI both in patients with or w/o bleeding

PREMIER database (2004–2008)
62,025 PCI procedures for STEMI

6946 pts were treated with bivalirudine and 55079 with Heparin + GPI
Matched 79% of pts with bivalirudine

Outcomes	Bivalirudin Treatment Group N=5,519	Heparin + GPI Treatment Group N=16,557	P-value (adjusted for matching)
Inpatient death, N (%)	217 (3.9%)	764 (4.6%)	0.0334
Severe bleed, N (%)	222 (4.0%)	920 (5.6%)	<0.0001
Length of stay, mean (SD), days	4.3 (4.6)	4.6 (4.9)	<0.0001
Cost, mean (SD), $	$18,799 ($15,632)	$20,511 ($18,011)	<0.0001

Pinto et al., ACC

Analyse médico-économique de la bivalirudine à l'HEGP

Real-world experience at a single center in France

- Consecutive series of 309 patients admitted for ACS at HEGP in 2010.
- Antithrombotic therapy was left at the discretion of the physician on duty
- Assessment of baseline characteristics, outcomes and costs according to use of bivalirudin

HEGP cohort: baseline characteristics (1)

	No bivalirudin (N=284)	Bivalirudin (N=25)	P Value
Age (years; mean	65.2 ± 13.3	67.2 ± 14.5	0.47
Sex (M) [n, (%)]	217 (76%)	18 (72%)	0.62
STEMI [n, (%)]	98 (34.5)	10 (40)	0.58
NSTE-ACS [n, (%)]	186 (65.5)	15 (60)	0.58
GRACE score	138 ± 35	141 ± 29	0.59

HEGP cohort: baseline characteristics (2)

	No bivalirudin (N=284)	Bivalirudin (N=25)	P Value
Diabetes	59 (21)	3 (12)	0.29
Hypertension	156 (55)	14 (56)	0.92
Hyperlipidemia	154 (54)	12 (48)	0.38
Current smoking	85 (30)	5 (20)	0.29
Family history	87 (31)	6 (24)	0.06
Prior AMI	46 (16)	2 (8)	0.28
Prior PCI	59 (21)	5 (20)	0.93
Prior CABG	19 (11)	0	
Prior stroke	5 (2)	0	0.50
History of heart	5 (2)	0	0.50
Peripheral artery	17 (6)	1 (4)	0.68
Chronic renal failure	24 (8.5)	0	0.13
COPD	5 (2)	0	0.50
Cancer	18 (6)	1 (4)	0.64

HEGP cohort: in-hospital management

	No bivalirudin	Bivalirudin	P Value
Pre-hospital medications			
SAMU called first	99 (35)	5 (20)	0.36
Aspirin	74 (26)	3 (12)	0.12
Clopidogrel	63 (22)	3 (12)	0.23
UFH	41 (14)	3 (12)	0.74
LMWH	26 (9)	0	0.11
Medications during first 48 h			
ASA	273 (96)	25 (100)	0.32
Clopidogrel	251 (88)	23 (92)	0.58
UFH	194 (68)	13 (52)	0.10
LMWH	210 (74)	21 (84)	0.27
Fondaparinux	24 (9)	1 (4)	0.69
Oral anticoagulants	14 (5)	1 (4)	0.84
GP IIB/IIIA inhibitors	95 (33.5)	1 (4)	0.002
Abciximab	79 (28)	0	0.002

HEGP cohort: procedural data

	No bivalirudin (N=284)	Bivalirudin (N=25)	P value
Access site (% femoral)	60 (21)	3 (12)	0.56
PCI	197 (69)	24 (96)	0.005
DES	59 (30)	11 (46)	0.11
BMS	120 (61)	14 (58)	0.81
PCI success	55 (28)	3 (12.5)	0.105
Closure device	181 (92)	23 (96)	0.49
CABG	38 (14)	3 (12.5)	0.60

HEGP cohort: in-hospital outcomes

	No bivalirudin	Bivalirudin	P value
Death	5 (1.8)	0	0.50
Re-MI	2 (0.7)	0	0.67
Recurrent ischemia	5 (1.8)	0	0.50
Death, re-MI or recurrent	12 (4.2)	0	0.29
Stroke	0	1 (4)	0.08
Minor bleeding	10 (3.5)	1 (4)	0.90
Major bleeding	2 (0.7)	0	0.67
Transfusion	17 (6)	0	0.21
Any bleeding or	22 (7.7)	1 (4)	0.49
All cardiac ischemic events	32 (11.3)	1 (4)	0.26

HEGP cohort: duration of hospital stay

	No Bivalirudin (N=284)	Bivalirudin (N=25)	P Value (Mann-Whitney)
Duration of stay in CCU (days; mean ± SD)	3.36 ± 2.48	2.72 ± 1.14	0.34
Duration of hospital stay (days; mean ± SD)	7.67 ± 9.64	4.24 ± 2.15	0.015
Population without CABG			
Duration of stay in CCU (days; mean ± SD)	3.28 ± 2.52	2.72 ± 1.14	0.43
Duration of hospital stay (days; mean ± SD)	6.74 ± 5.80	4.24 ± 2.15	0.04

Transfusion was associated with an increase in length of stay (patients w/o CABG)

CCU: 4.24 ± 2.77 vs 3.17 ± 2.41, P=0.08

Overall hospital stay: 12.2 ± 7.4 vs 6.2 ± 5.3, P<0.001)

HEGP cohort: cost analysis

	No bivalirudin	Bivalirudin	P Value
Cost ICU	8,441 ± 6,320	6,944 ±	0.34
Cost Cardiology ward	5,004 ± 10,491	1,741 ±	0.024
Total cost of hospitalisation	**13,445 ±**	**8,686 ±**	**0.020**
Abciximab	**338 ± 643**	**0**	**0.006**
Tirofiban	1.41 ± 16.8	0	0.67
Eptifibatide	6.87 ± 29.1	5.20 ± 26.0	0.78
Red blood cells transfusion	23 ± 97	0	0.21
Bivalirudin	1.44 ± 24.2	408 ± 0	<0.001
Closure device	20 ± 52	18 ± 51	0.85
Total medication cost	391 ± 642	432 ± 55	<0.001
Overall cost	**13,835 ±**	**9,118 ±**	**0.046**

Conclusion: HEGP registry

- In our real world experience, using bivalirudin in ACS patients intended for an invasive strategy was associated with non significantly fewer ischemic and bleeding events.
- Cost analysis showed that the overall medication cost was marginally higher for bivalirudin-treated patients, mainly because abciximab was not used, and reduced overall costs related to shorter hospital stays.
- Although these results are encouraging, it must be pointed out that they result from non randomised comparisons and are subject to potential bias.

Bivalirudine, évaluation ME, synthèse

- L'utilisation de la bivalirudine, dans les indications cliniques recommandées (SCA), apparait comme une stratégie dominante (moins coûteuse et plus efficace sur un critère clinique composite efficacité-sécurité) par rapport à l'association héparinothérapie – GPI

- Ce résultat apparait robuste à la fois en fonction de l'indication clinique (SCA ST- à risque élevé ou à risque modéré, SCA ST+), de la nature de l'évaluation ME (étude randomisée ou modélisations), et du système de soins (US ou France).

Economic Evaluation of Fractional Flow Reserve–Guided Percutaneous Coronary Intervention in Patients With Multivessel Disease

William F. Fearon, MD; Bernhard Bornschein, MD, MPH; Pim A.L. Tonino, MD, PhD; Raffaella M. Gothe, BS; Bernard De Bruyne, MD, PhD; Nico H.J. Pijls, MD, PhD; Uwe Siebert, MD, MPH, MSc, ScD; for the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) Study Investigators

Conclusion: « Economic evaluation of the FAME study reveals that FFR-guided percutaneous coronary intervention in patients with multivessel coronary disease is one of those rare situations in which a new technology not only improves outcomes but also saves resources ».

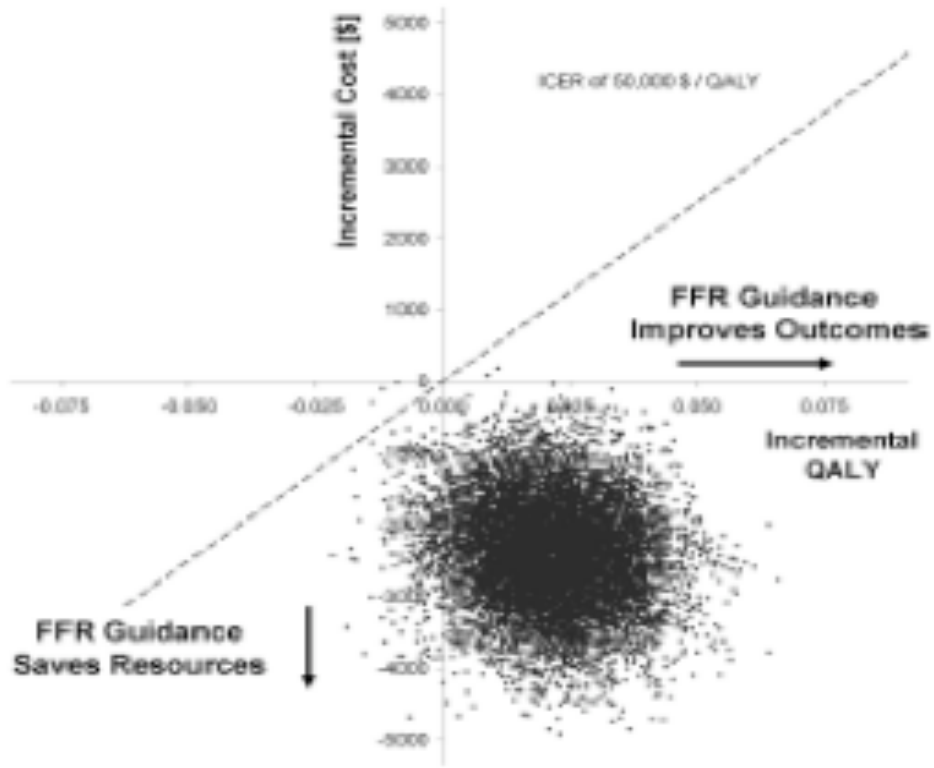


Figure 1. Bootstrap simulation of incremental costs and effects.

Compared direct cost of enoxaparin and bivalirudin

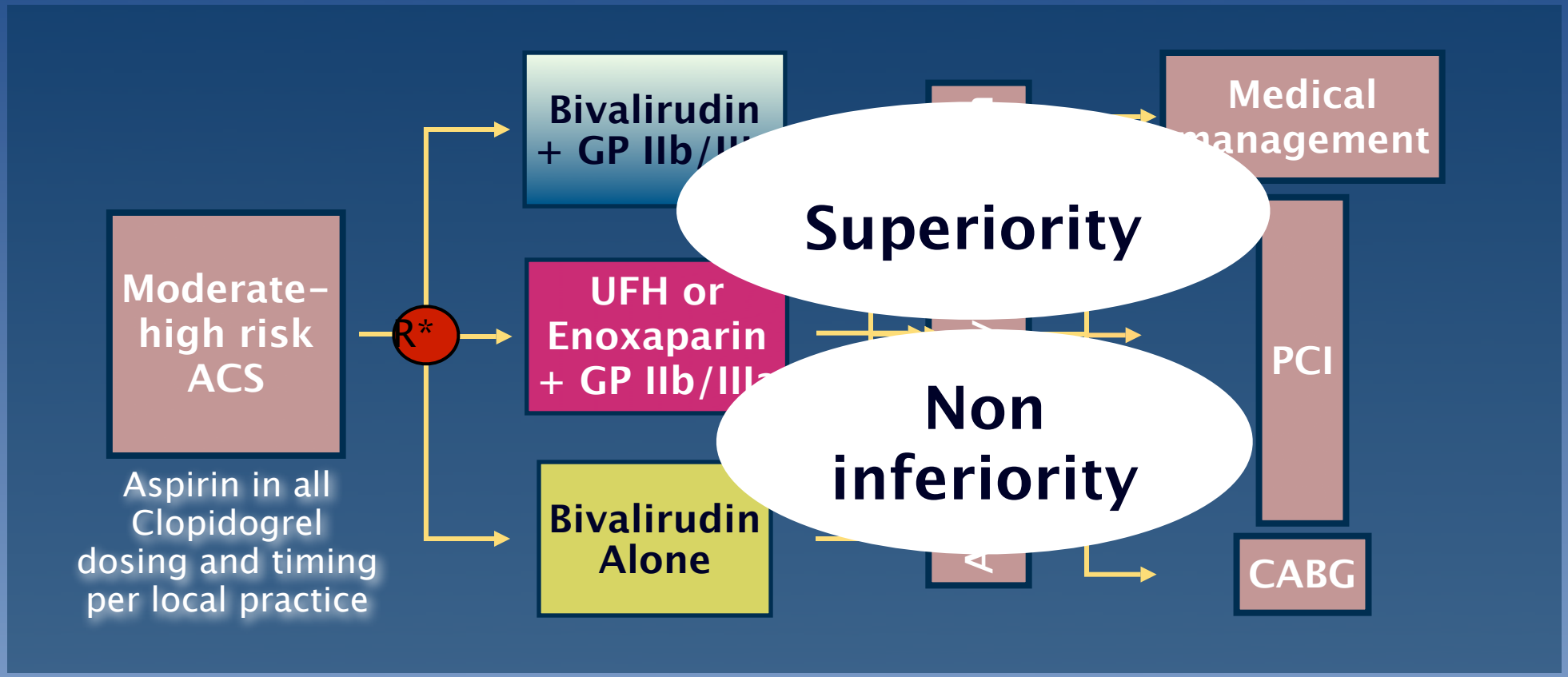
✓ **ENOXAPARIN 8000 UI anti-Xa/0,8 ml** : solution injectable ; boîte de 2 seringues préremplies avec système de sécurité
Liste I – Remboursable à 65 % – **Prix : 20,07 €**

⟹ **For 2 days: 40.14 €**

✓ **BIVALIRUDIN 250 mg:** ⟹ **408.00 €**

ACUITY trial: compared costs

Moderate-high risk unstable angina or NSTEMI undergoing an invasive strategy (N = 13,800)

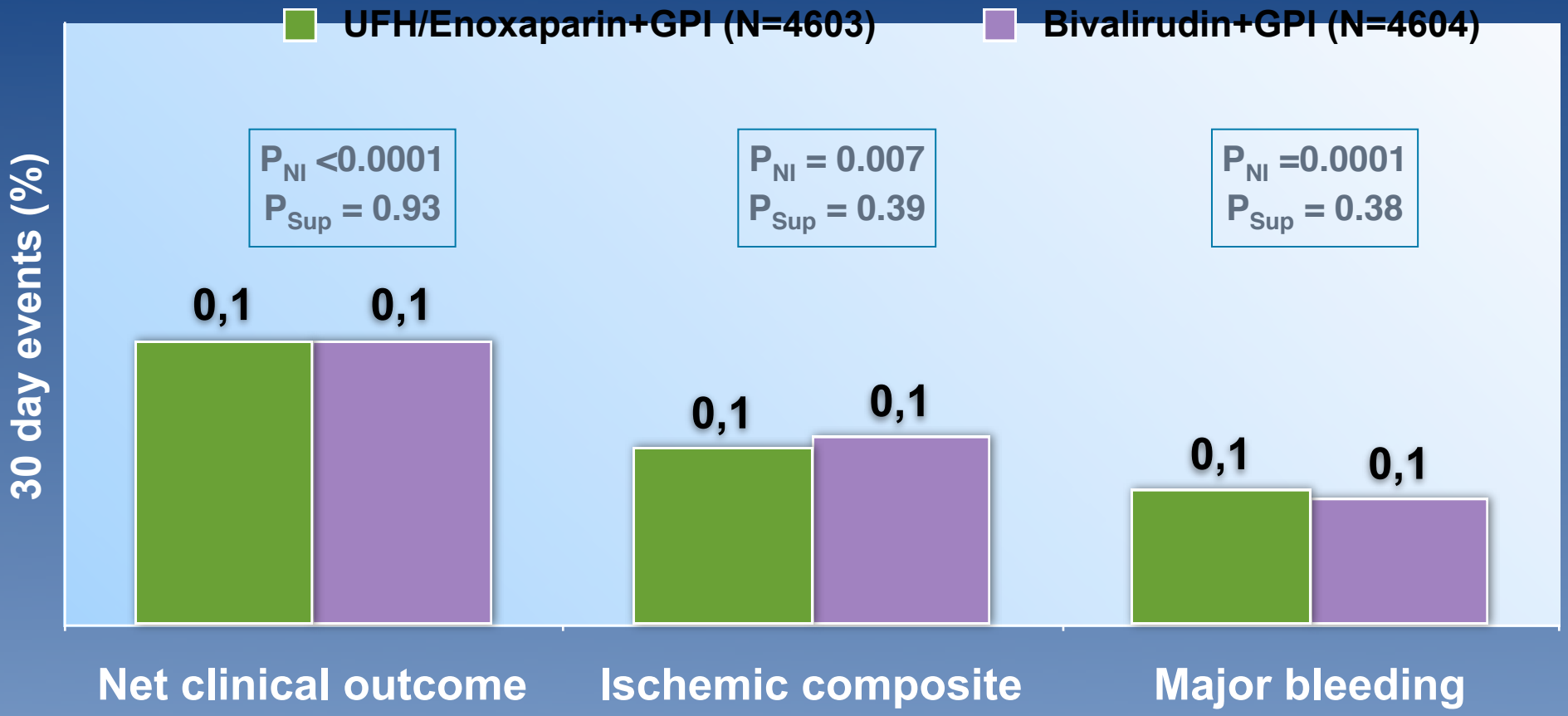


*Stratified by pre-angiography thienopyridine use or administration

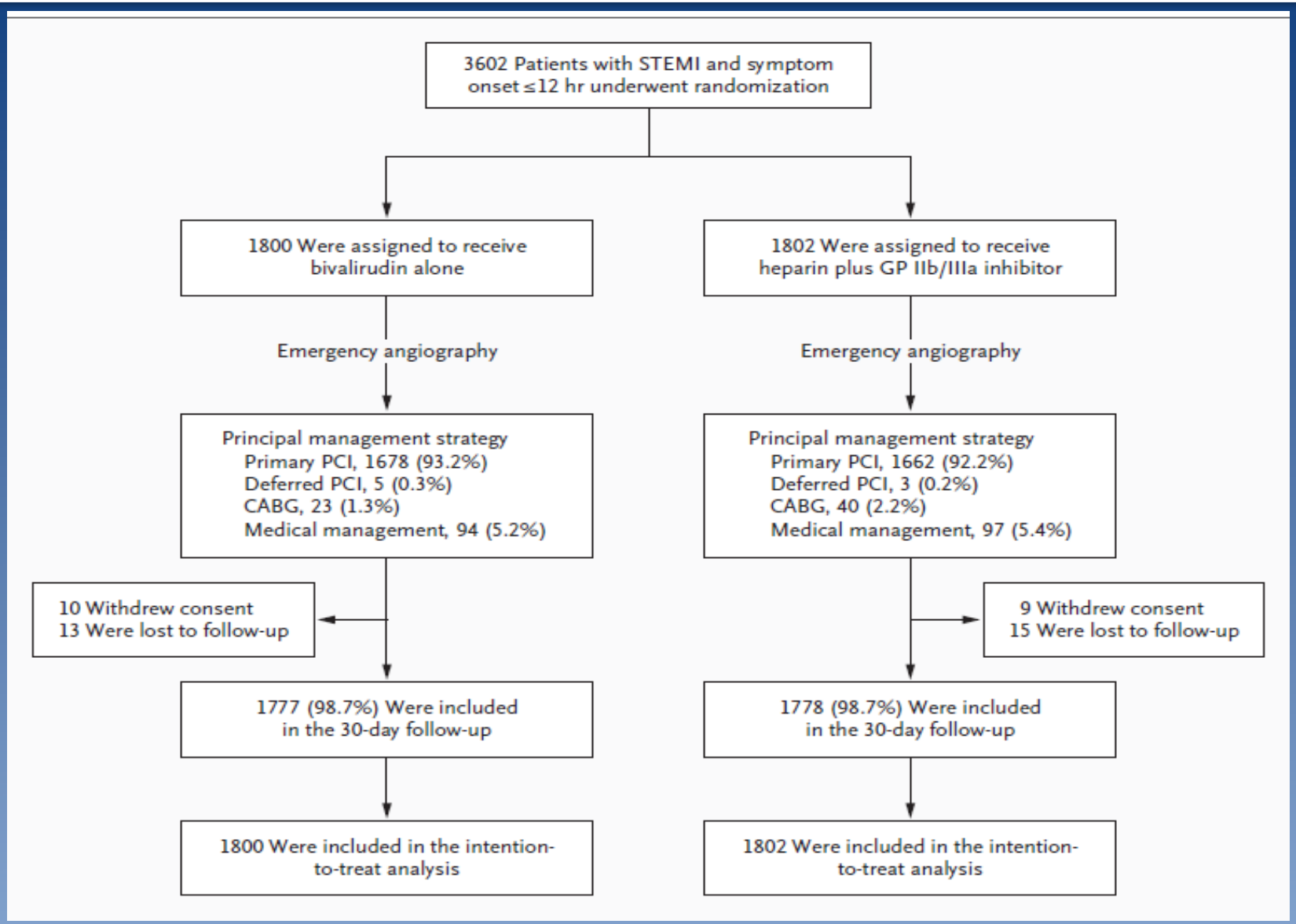
ACUITY Design. Stone GW et al. AHJ 2004;148:764-75

Primary Endpoint Measures (ITT)

UFH/Enoxaparin + GPI vs. Bivalirudin + GPI

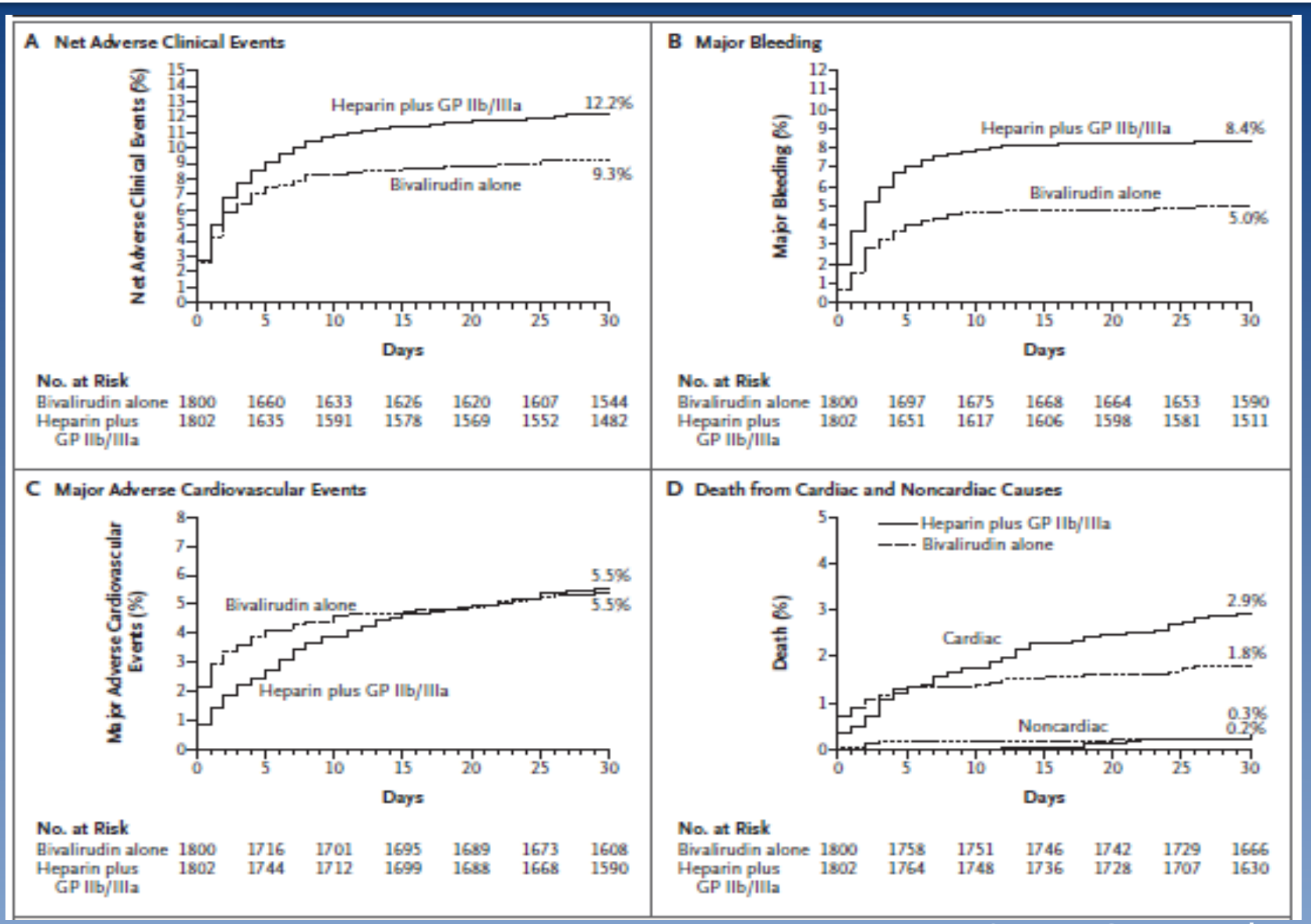


HORIZONS trial: study flow chart



Stone GW, et al. NEJM 2008

HORIZON trial: results



Stone GW, et al. NEJM 2008

Real-world US data: the PREMIER database

- A comprehensive repository of clinical, financial, and outcomes information that undergo routine quality and completeness checks including data verification, reconciliation, and validation
- Used by the FDA for drug surveillance and by CMS to evaluate next-generation payment models
- Over 5 million inpatient discharges and over 30 million hospital outpatient visits are recorded annually; approximately 1/6 of all US hospitalizations
- Potential to allow greater insight on comparative effectiveness issues

Data: Bajaj et al. TCT 2010

PREMIER database: 2004–2008

- Patients stratified in four groups: BIV, BIV+GPI, HEP, and HEP+GPI.
- Multivariate analysis (MVA) was used to adjust for confounding patient and hospital covariates.
- Logistic regression models of in-hospital mortality were developed. Covariates included: patient demographics, admission year, diagnosis (STEMI, non-STEMI, unstable angina, stable angina, chronic ischemic heart disease(CIHD)), insurance payor, hospital characteristics (region, rural/urban, teaching status, and bed size), patient co-morbidities, concomitant medication use, procedural information, and bleeding complications.
- MVA were conducted for (1) all patients, (2) those with bleeding complications, and (3) those without bleeding complications.

Data: Bajaj et al. TCT 2010

Bleeding in the NCDR

Composite bleeding endpoint:

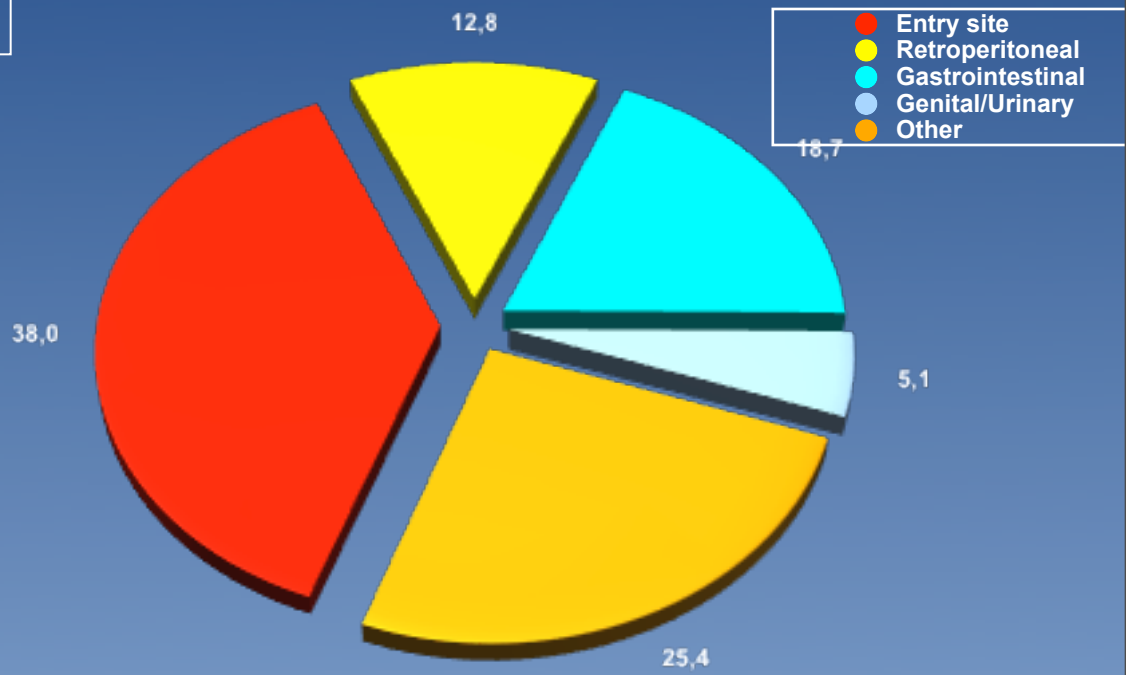
- Requiring transfusion
- Prolonged hospital stay, and/or
- Decrease in hemoglobin >3 g/dL

Occurring at:

- Entry site
- Retroperitoneal
- Gastrointestinal
- Genitourinary
- Other/unknown location

NCDR:

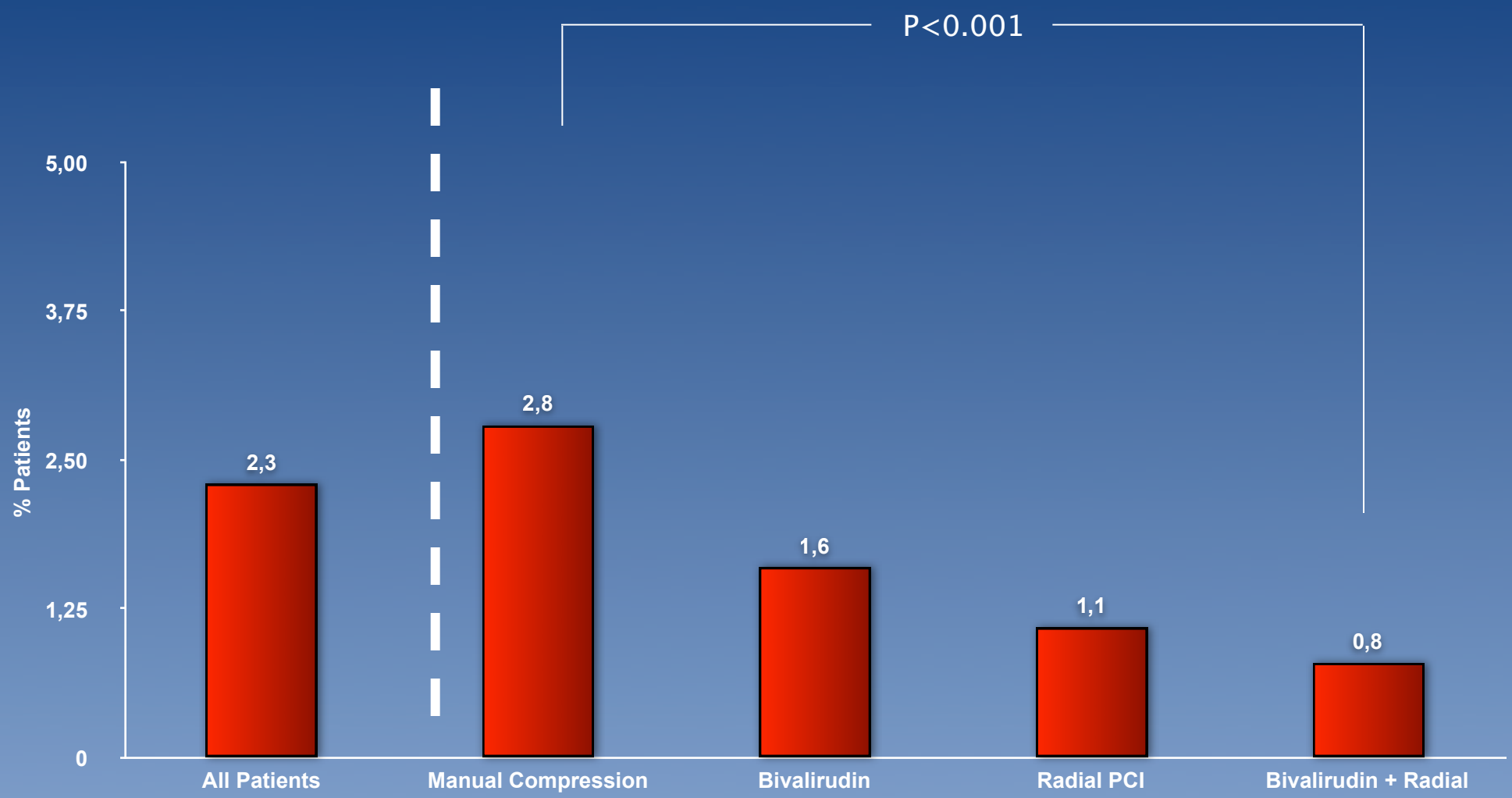
- 1,522,935 PCI procedures
- 955 US Centers
- Total bleeds: n=30,654
- Percent bleeds: 2.0%



Marso et al. JAMA 2010;303:2156-64

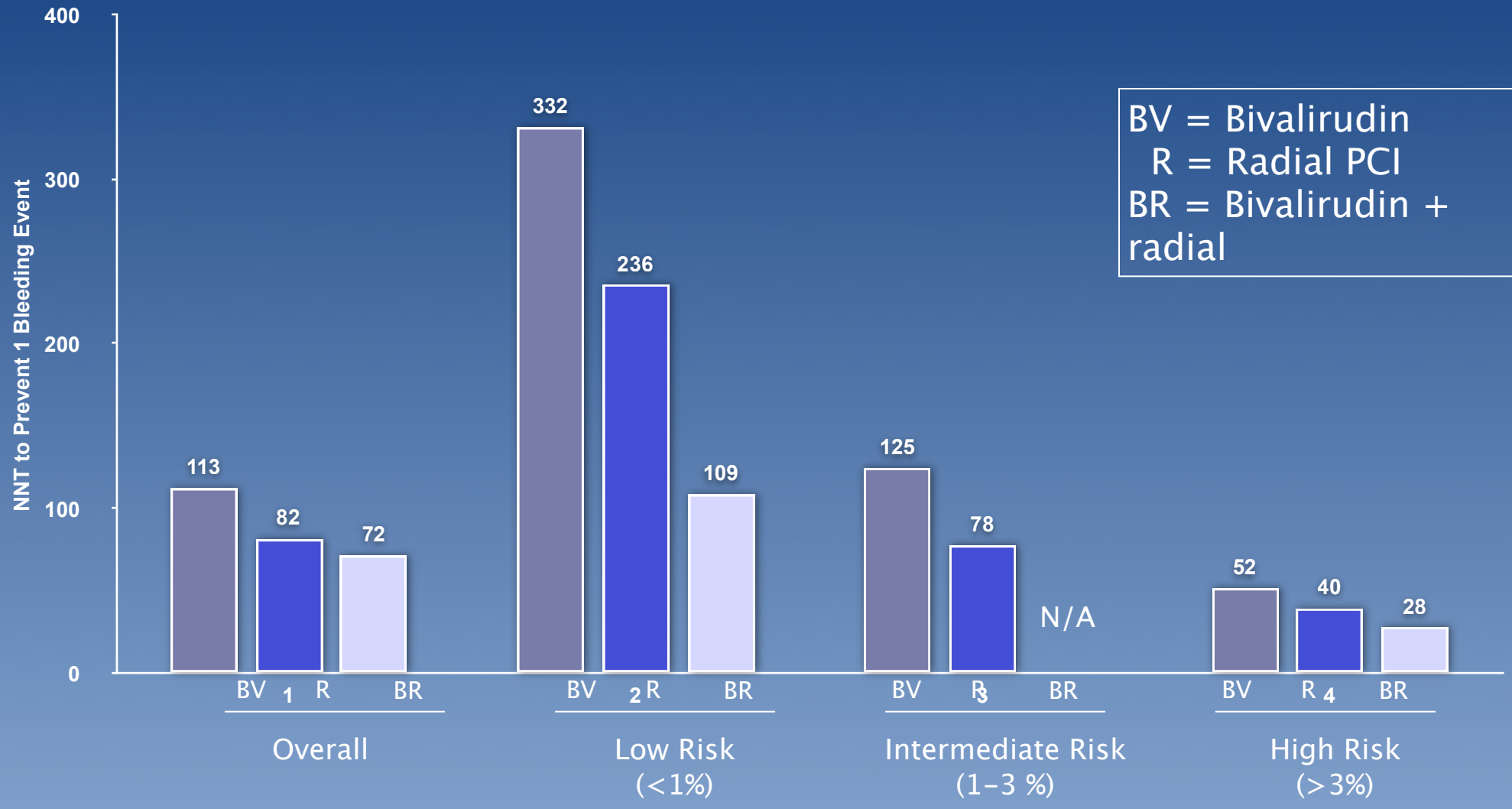
Bleeding

N=982,077



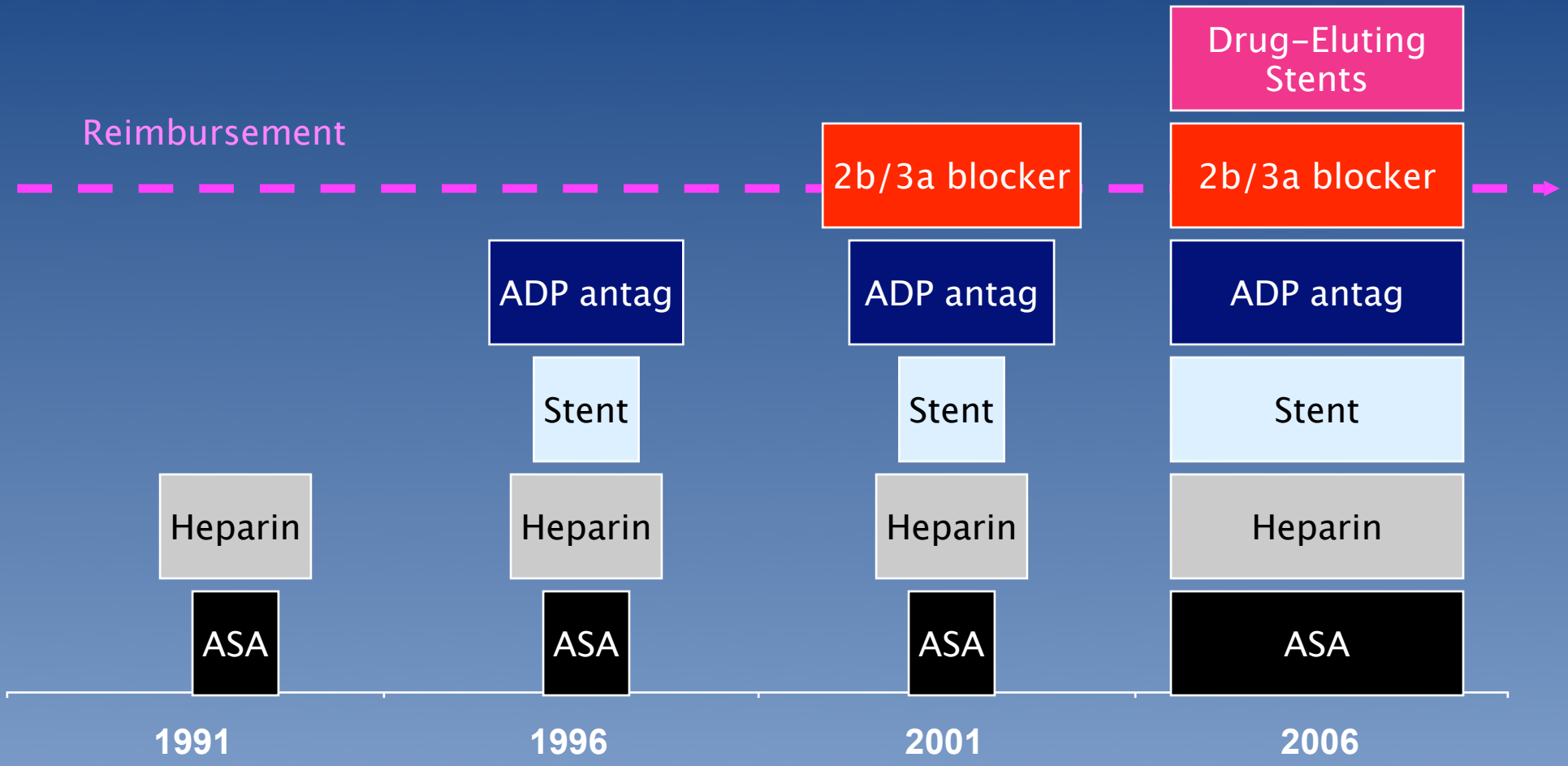
Marso et al. ACC/i2 Scientific Sessions 2010; abstract 2505-458

Number Needed to Treat (NNT) to Prevent 1 Bleeding Event



Marso et al. ACC/i2 Scientific Sessions 2010; abstract 2505-458

Economics of PCI: Hospital Perspective



Cost of Complications in ACS: ACUITY

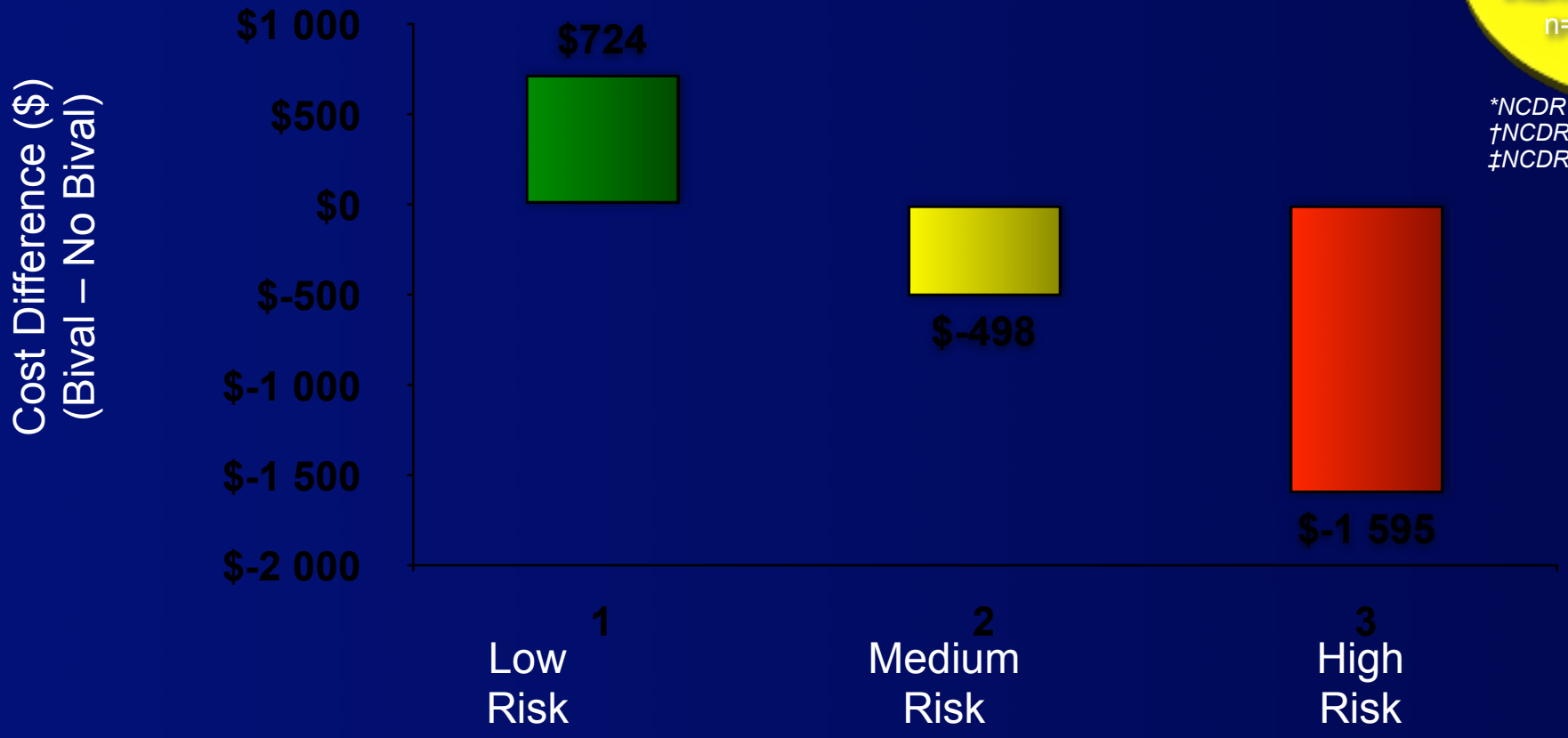
Complication	Incre C		Attributable Cost
Death	$8958	0.5%	$49
MI	$3334	4.8%	$160
Unplanned Revasc	$12,224	0.9%	$110
Major bleed	$7278	4.8%	$342
Minor bleed	$2122	24.5%	$509

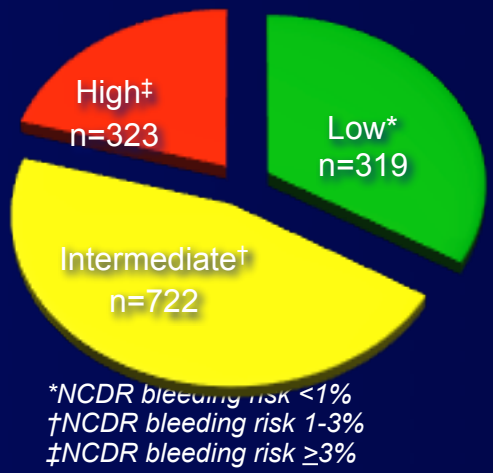
Bleeding complications accounted for $851 per patient of additional costs

* Also adjusted for age, gender, diabetes, and type of planned revascularization

Cohen: TCT 2006

Incremental Cost Effectiveness of Bivalirudin: Strata by Bleeding Risk





Lindsey et al. EuroIntervention 2010;6:206-213