PERIOPERATIVE MANAGEMENT OF OAT AND AP IN NC SURGERY

ASA, anti $P2Y_{12}$, DAPT

OAT, NOA

WHY ?

What we know

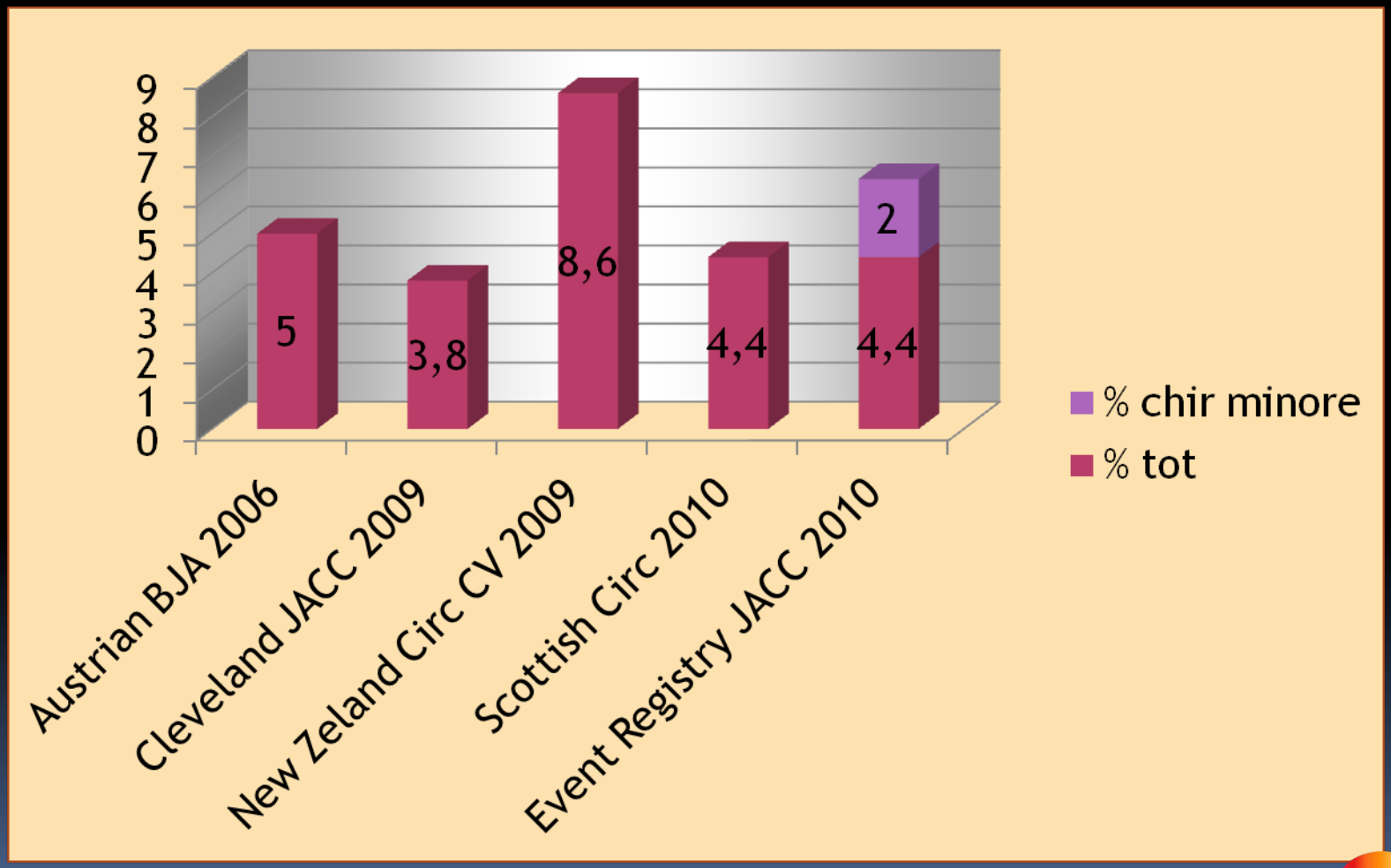
Table 7—*Annualized Risk of Thrombotic Complications in the Absence of Anticoagulant Therapy for Selected Conditions*[179]

Condition	Annualized Thrombosis Risk, %
Lone atrial fibrillation	1
Average risk atrial fibrillation	5
High-risk atrial fibrillation	12
Dual-leaflet (St. Jude) aortic valve prosthesis	10–12
Single-leaflet (Bjork-Shiley) aortic valve prosthesis	23
Dual-leaflet (St. Jude) mitral valve prosthesis	22
Multiple St. Jude prostheses	91

The 7° ACCP conference on AT Therapy Chest 2004; 126: 204S

We have non data about incidence of TE events during WD of OAT
15% mechanical prosthesis thrombosis is fatal
70% of emorrhagic stroke leads to death/severe disability

Incidence of surgery within 1 year after coronary stenting



The Dimensions of the Problem

Country	Year	Numbers	Source
USA	2006	1,100,000 PCI on 622.0[illegible]s	Roger VL. Heart disease and stroke statistics 2011. Circulation 2011
Europe	2006		Moschovitis A. PCI in Europe 2006. Eur Heart J 2010
Italy	201[illegible]	**139,263**	www.gise.it Accessed 11.09.2012
Lombardia	2011	22,467	www.gise.it Accessed 11.09.2012

5600 pts

GUIDELINES

In the 2009 ESC gl on perioperative management for non cardiac surgery only few pages for ASA-DAPT –OAT discontinuation.

The majority of pages are dedicated to clinical risk stratification

Only cardiologist had new GL on the basis of new anti platelet / anticoagulant therapy
The last anaestesiogical GL are: 2001 ESRA, 2002 ASRA and SIARTI,
The last FCSA GL are on 2005

ASA, P2Y blocker

What, When, How

Thrombotic Risk profile (cardiologist, others)

Haemorragic Risk Profile (surgeon)

	Low	Intermediate	High
Low			
Intermediate			
High			

Therapeutic STRATEGY

Indipendent predictors of cardiac and bleeding events within NCS

- LVEF at surgery admission
- HB at surgery admission
- ID -Diabetes
- DAPT
- ASA discontinuation
- DAPT discontinuation > 5 days before NCS
- OAT
- DAPT
- Bridging Therapy (LMWH)

Rossini R et al ESC 2012 – polycentric, retrospective study on 670 pts

TE RISK X NCS: DEFINITION

- LOW : breast, dental, endocrine, eye gynecology, reconstructive, minor orthopedic and minor urologic
- INTERMEDIATE: Abdominal, carotid, peripheral PTA, endovascular repair, head and neck surgery, neurological-orthopedic major, urological major, pulmonary, renal, liver transplant
- HIGH: aortic and major vascular, peripheral major.

TE RISK X CHD: DEFINITION

LOW RISK

- > 6 m PCI/BMS
- > 12 m PCI/DES

INTERMEDIATE RISK

- 1 - 6 m PCI/BMS
- 6 -12 m PCI/DES
- > 12 m PCI/DES at high risk: Lengh, multiple, overlapping, < 2 mm diameter, last remaning vessel, LMCA
- 1-6 m CABG or ntACS

HIGH RISK

- < 1 m PCI/BMS
- < 6 m PCI/DES
- < 12 m DES at risk
- < 1 m CABG or ntACS

ST risk arises if: ACS during procedure, re-do, EF < 35%, CRI, MD;

POBA: are at high risk within 2 w, intermediate 2-4 w, low > 4 w

Aspirin discontinuation

European Heart Journal (2006) 27, 2667–2674
doi:10.1093/eurheartj/ehl334

Clinical research
Coronary heart disease

A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50 279 patients at risk for coronary artery disease

Giuseppe G.L. Biondi-Zoccai[1*], Marzia Lotrionte[2], Pierfrancesco Agostoni[3], Antonio Abbate[4], Massimiliano Fusaro[5], Francesco Burzotta[2], Luca Testa[1], Imad Sheiban[1], and Giuseppe Sangiorgi[6]

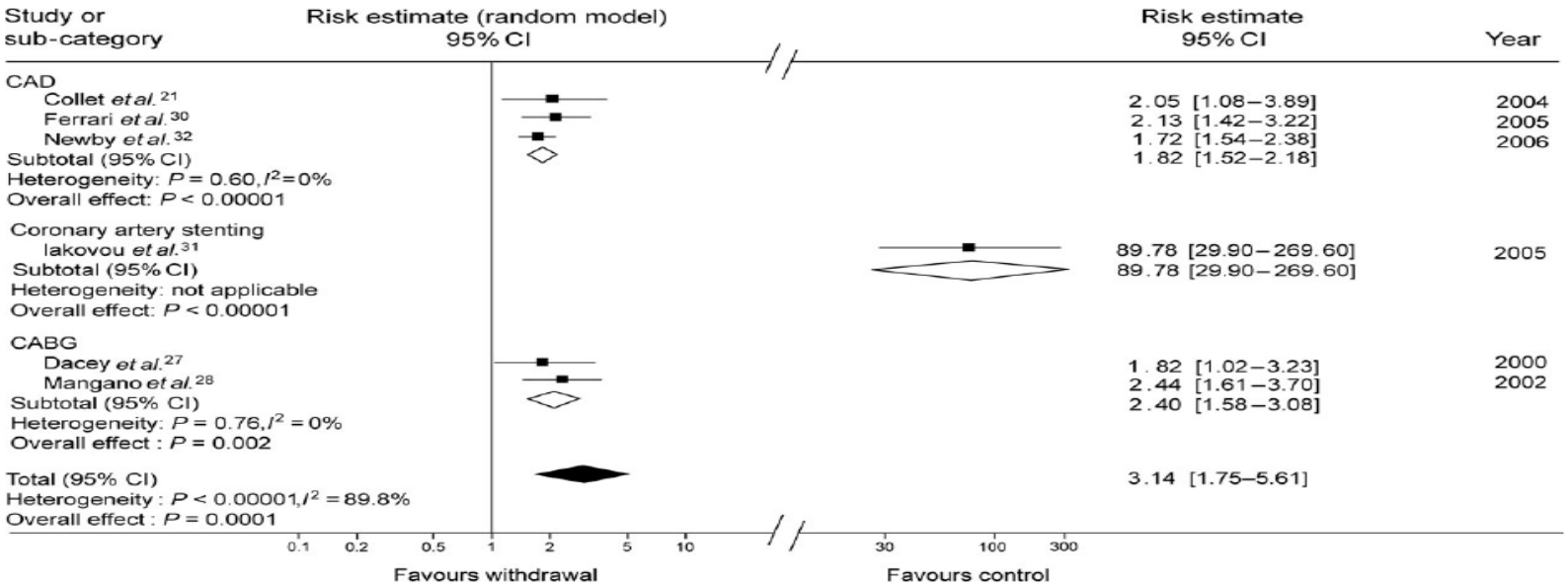
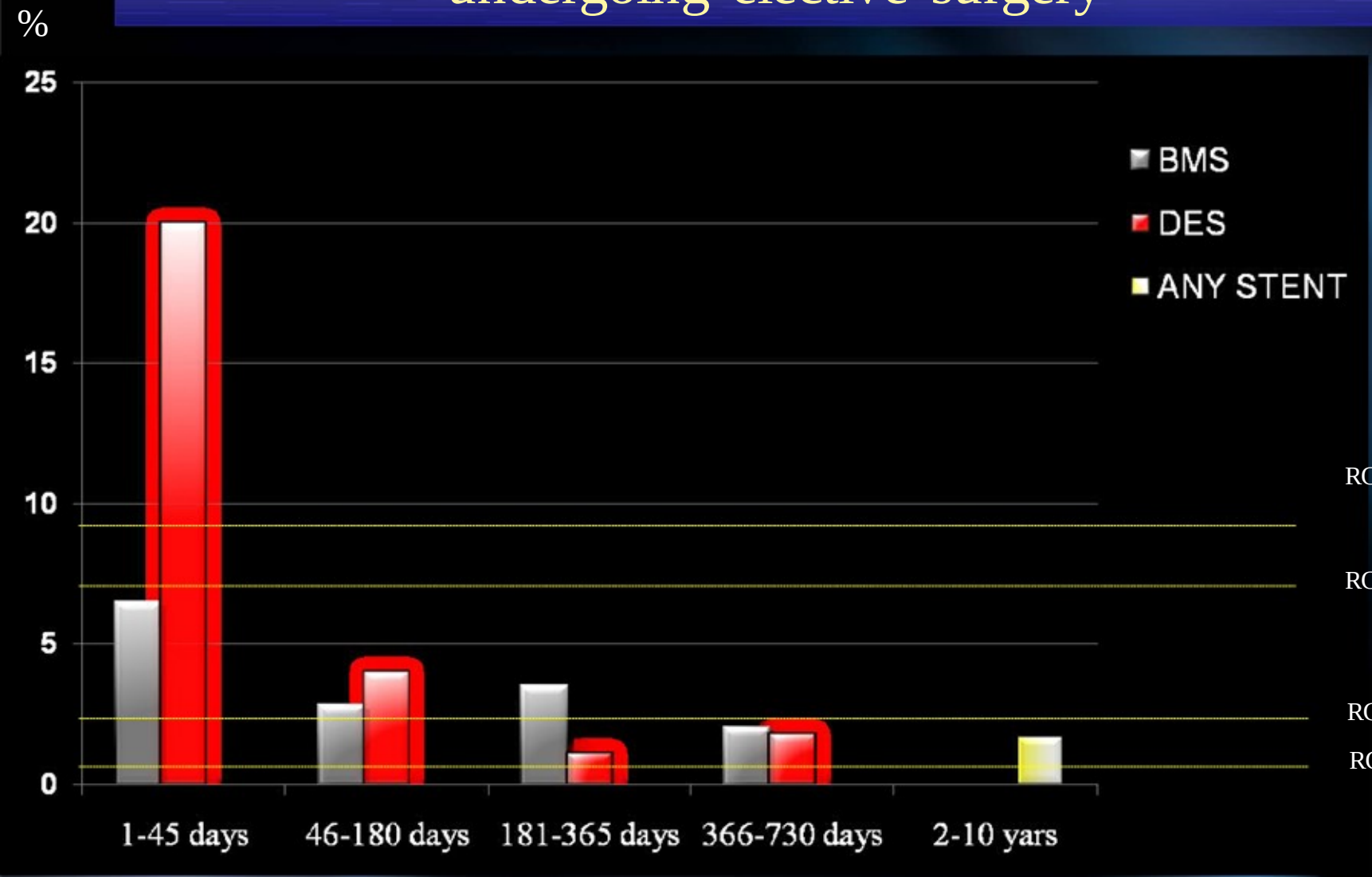


Figure 2 Forest plot of the risk of adverse thrombotic events in patients not adhering to or discontinuing aspirin. The analysis is stratified according to the clinical setting and follow-up duration. There is a statistically significant association between aspirin discontinuation and adverse clinical outcome overall, and in each subgroup. While every subgroup appears clinically and statistically homogeneous, the risk of antiplatelet discontinuation appear far greater after PCI with drug-eluting stent implantation, as reported by Iakovou *et al.*,[31] than in any other study group.

MACE at 30 days in patients with coronary stent undergoing elective surgery



RCRI ≥ 4: 9.7%

RCRI 3 : 6.3%

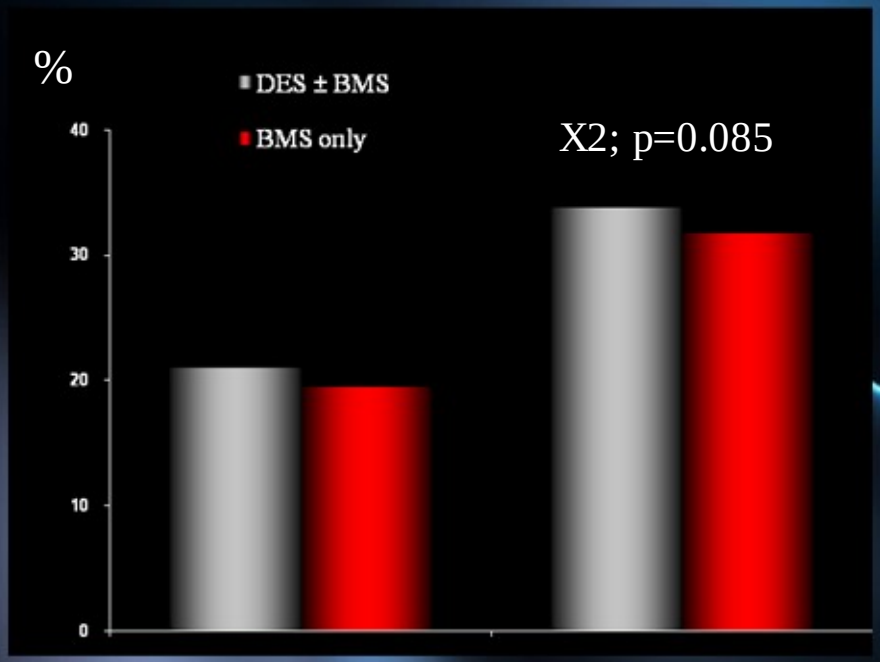
RCRI 2: 3%

RCRI 1: 1.1%

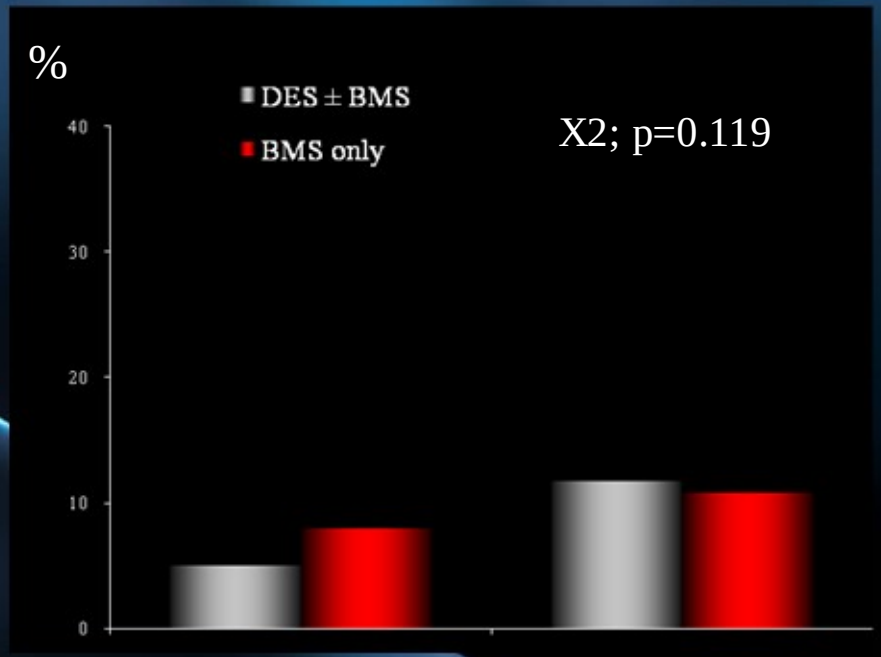
Wijeysundera D N et al. Circulation 2012;126:1355-1362

MACCE according to preoperative interruption in antiplatelet therapy in DES (±BMS) and BMS (only) stented patients in high- and low-risk surgery

High risk surgery

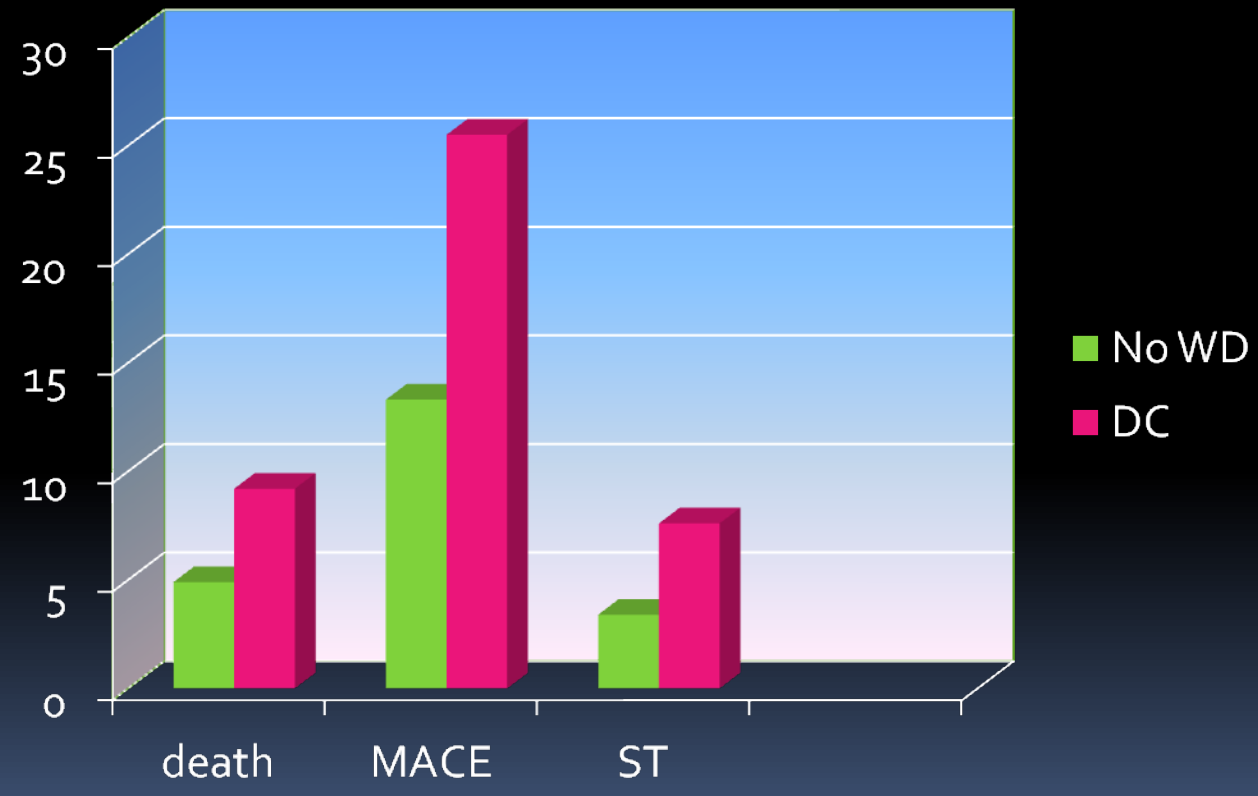


Low risk surgery



P. Albaladejo et al Heart 2011;97:1566-1572

Discontinuation and prognosis



Rossini R et al Am J Cardiol 2011, 107: 186-194

Cardiovascular risks after low-dose aspirin perioperative withdrawal versus bleeding risks with its continuation

Meta-analysis of 41 studies (12 observational retrospective, 19 observational prospective, 10 randomized), including 49 590 patients (14 981 on aspirin, 34 609 controls).

Aspirin multiplied baseline bleeding rate: x 1.5 (1.0-2.5)

Perioperative mortality, caused by bleeding, is not affected by ASA

Only in transurethral prostatectomy mortality possibly related to bleeding increase

Eur GL 2009

What the guidelines say (and don't say)

Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery

Recommendations on aspirin

Recommendations	Class[a]	Level[b]
Continuation of aspirin in patients previously treated with aspirin should be considered in the perioperative period	IIa	B
Discontinuation of aspirin therapy in patients previously treated with aspirin should be considered only in those in whom haemostasis is difficult to control during surgery	IIa	B

Eur Heart J. 2009;30:2769-812

How and When: ASA and P2Y blocker

Table 5 Proposal for perioperative antiplatelet management based on patient's risk of thrombosis vs. surgical bleeding risk

Surgical bleeding risk	Patient's thrombotic risk		
	Low: >9–12 months after uncomplicated ACS, DES, POBA, BMS, CABG	Medium: 7 weeks to 9–12 months after uncomplicated ACS, POBA, BMS, CABG; 7–12 months after DES, or high-risk stent	High: ≤6 weeks after ACS, POBA, BMS, CABG, or <9–12 months after their complications; ≤6 months after DES or high-risk stent
Low (transfusion usually not needed): general biopsies. skin, dental, anterior eye, minor general, minor orthopaedic, minor ENT surgery, endoscopy	Maintain low-dose aspirin	Maintain low-dose aspirin and $P2Y_{12}$ blocker (if prescribed)	Maintain low-dose aspirin and $P2Y_{12}$ blocker (if prescribed)
Medium (transfusion often required): cardiovascular, visceral, ENT, reconstructive, major orthopaedic, endoscopic urological surgery	Maintain low-dose aspirin	Maintain low-dose aspirin and $P2Y_{12}$ blocker (if prescribed)	Maintain low-dose aspirin and $P2Y_{12}$ blocker (if prescribed)
High: intracranial, spinal canal, posterior eye surgery. Possible bleed in closed space. Large expected blood loss	Withdraw aspirin for 3–5 days	Postpone elective surgery. If urgent, maintain low-dose aspirin for all but intracranial surgery. Withdraw $P2Y_{12}$ blocker (if prescribed) for 5 days[a]	Postpone non-vital surgery. If vital, maintain low-dose aspirin. Withdraw $P2Y_{12}$ blocker (if prescribed) for 5 days.[a] Consider bridging with small molecule i.v. GPI

Individual characteristics that enhance bleeding risk (e.g. age, renal failure) are not considered here but are discussed elsewhere. Withdrawal of aspirin is recommended for only one, and or $P2Y_{12}$ blockers for two, of the nine combinations. Because stroke patients may receive aspirin alone, aspirin + dipyridamole, or clopidogrel alone, their management is not discussed, nor are there sufficient data to make specific recommendations.

artery bypass graft; DES, drug-eluting stent; ENT, ear nose and throat; GPI, glycoprotein IIb/IIIa inhibitor.

individual agent; however, comparative data among the three available $P2Y_{12}$ blockers are lacking.

European Heart Journal (2011) 32, 2922–2932
doi:10.1093/eurheartj/ehr373

REVIEW

Frontiers in cardiovascular medicine

Antiplatelet agents for the treatment and prevention of atherothrombosis

Carlo Patrono[1*], Felicita Andreotti[2], Harald Arnesen[3], Lina Badimon[4], Colin Baigent[5], Jean-Philippe Collet[6], Raffaele De Caterina[7], Dietrich Gulba[8], Kurt Huber[9], Steen Husted[10], Steen Dalby Kristensen[11], João Morais[12], Franz-Josef Neumann[13], Lars Hvilsted Rasmussen[14], Agneta Siegbahn[15], Philippe-Gabriel Steg[16], Robert F. Storey[17], Frans Van de Werf[18], and Freek Verheugt[19†]

Presidio Sanitario Gradenigo

OAT

Risk stratification

Clinical: Valvular Prothesis, FE, LA volume,
non cardiac condition (neurological, renal thyroid,liver)

Arrhytmic: tipe, duration , long-standing

CHA2DS2 Vasc score and HASBLED

Traditional Bridge therapy with UFH

1. Stop OAT 4 – 5 ds before surgery
2. Admission of pt for UHF ev therapy
3. Stop UHF infusion 3 – 4 h before surgery
4. Restart UHF 12-24 h after surgery and OAT as soon as possibile, maintaining UHF ev till INR in range
5. Stop UHF ev

- LMWH totally modified this management

DOUKETIS protocol 2004 (EBPM)

- STOP OAT 5 ds before surgery if INR 2-3 or 6 ds if INR > 3
- • Control INR 3 ds before surgery:
- - if INR < 2.5 → dalteparina 100 U/kg x 2/d
- - if INR > 2.5 → vit. K 1 mg p.o.
- - last dose of dalteparina 12 h before surgery
- • restart OAT:
- - High haemorragic risk → the evening after surgery; NO dalteparina
- - Low " " → The same evening of surgery + dalteparina
- 100 U/kg 24 h after, TID
- • Stop dalteparina when INR ~ 2
- • Follow up for 7 d

Arch Intern Med 2004; 164: 1319-1326

ESC GL 2009: Bridge

Low thromboembolic risk / low bleeding risk

- Continue anticoagulant therapy with INR in therapeutic range.

Low thromboembolic risk / high bleeding risk

- Discontinue anticoagulant therapy 5 days before the procedure.
- Start LMWH prophylaxis once daily or **UFH i.v.** 1 day after acenocoumarol interruption, and 2 days after warfarin interruption. Administer the last dose of LMWH at least 12 h before the procedure or give **UFH i.v.** up to 4 h prior to surgery.
- Resume LMWH or UFH at the pre-procedural dose 1–2 days (at least 12 h) after the procedure according to haemostatic status. Resume anticoagulant therapy 1 to 2 days after surgery at the pre-procedural dose + 50% boost dose for two consecutive days according to the haemostatic status.
- LMWH or UFH is continued until the INR has returned to therapeutic levels.

High thromboembolic risk

- Discontinue anticoagulant therapy 5 days before the procedure.
- Start therapeutic LMWH twice daily or **UFH i.v.** 1 day after acenocoumarol interruption, and 2 days after warfarin interruption. Administer the last dose of LMWH at least 12 h before the procedure or give **UFH i.v.** up to 4 h prior to surgery.
- Resume LMWH or UFH at the pre-procedural dose 1–2 days (at least 12 h) after the procedure according to haemostatic status. Resume anticoagulant therapy 1–2 days after surgery at the pre-procedural dose + 50% boost dose for two consecutive days according to haemostatic status.
- LMWH or UFH is continued until the INR has returned to therapeutic levels.

Hight Risk: FA,
protesi meccaniche,
protesi biologiche mitraliche
o riparazione < 3m
TVP/TEP < 3 m + trombofilia

	Patients at high thromboembolic risk		Patients at low thromboembolic risk	
Weight, kg	Nadroparin (twice daily, s.c.) (IU)	Enoxaparin (twice daily, s.c.) (IU)	Nadroparin (once daily, s.c.) (IU)	Enoxaparin (once daily, s.c.) (IU)
<50	2850	2000	2850	4000
50–69	3800	4000	3800	4000
70–89	5700	6000	5700	4000
90–110	7600	8000	5700	4000
>110	9500	10 000	5700	4000


NOA

NOA

	Dabigatran (RE-LY)[78,79]	Rivaroxaban (ROCKET-AF)[80]	Apixaban (ARISTOTLE)[81]
Drug characteristics			
Mechanism	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor
Bioavailability, %	6	60–80	50
Time to peak levels, h	3	3	3
Half-life, h	12–17	5–13	9–14
Excretion	80% renal	33 (liver), 33 renal	25% renal, 75% faecal
Dose	150 mg b.i.d.	20 mg o.d.	5 mg b.i.d.
Dose in renal impairment	110 mg b.i.d.	15 mg o.d. (if CrCl 30–49 mL/min)	2.5 mg b.i.d.
Special considerations	Intestinal absorption is pH-dependent and is reduced in patients taking proton-pump inhibitors	Higher levels expected in patients with renal or hepatic failure	
	Increased risk of bleeding in patients taking verapamil, amiodarone, quinidine, or ketoconazole	Activity lower in frail patients so should be taken after food	
Study design	Randomized, open-label	Randomized, double-blind	Randomized, double-blind
Number of patients	18 111	14 264	18 201
Follow-up period, years	2	1.9	1.8
Randomized groups	Dose-adjusted warfarin vs blinded dose of dabigatran (150 mg b.i.d., 110 mg b.i.d.)	Dose-adjusted warfarin vs rivaroxaban 20 mg o.d.	Dose-adjusted warfarin vs apixaban 5 mg b.i.d.
Age, years	71.5 ± 8.7 (mean ± SD)	73 (65–78) [median (interquartile range)]	70 (63–76) [median (interquartile range)]
Male sex, %	63.6	61.3	64.5
$CHADS_2$ (mean)	2.1	3.5	2.1
	Warfarin (n=6022)	Dabigatran 150 (n=6076)	Dabigatran 110 (n=6015)
		(RR, 95% CI; P value)	(RR, 95% CI; P value)
Stroke/systemic embolism	1.69	1.11 (0.66, 0.53–0.82; P for superiority <0.001)	1.53 (0.91, 0.74–1.11; P for non-inferiority <0.001)
Ischaemic stroke	1.2	0.92 (0.76, 0.60–0.98; P=0.03)	1.34 (1.11, 0.89–1.40; P=0.35)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; P<0.001)	0.12 (0.31, 0.17–0.56; P<0.001)
Major bleeding	3.36	3.11 (0.93, 0.81–1.07; P=0.31)	2.71 (0.80, 0.69–0.93; P=0.003)
Intracranial bleeding	0.74	0.30 (0.40, 0.27–0.60; P<0.001)	0.23 (0.31, 0.20–0.47; P<0.001)
Extracranial bleeding	2.67	2.84 (1.07, 0.92–1.25; P=0.38)	2.51 (0.94, 0.80–1.10; P=0.45)

	Rivaroxaban (n=7133)	Warfarin (n=7131)	Warfarin (n=9081)	Apixaban (n=9120)
		(HR, 95% CI; P value)		(HR, 95% CI; P value)
Stroke/systemic embolism	2.4	2.1 (0.88, 0.75–1.03; P for non-inferiority <0.001; P for superiority =0.12) (ITT)	1.6	1.27 (0.79, 0.66–0.95; P<0.001 for non-inferiority; P=0.01 for superiority)
Ischaemic stroke	1.42	1.34 (0.94, 0.75–1.17; P=0.581)	1.05	0.97 (0.92, 0.74–1.13; P=0.42)
Haemorrhagic stroke	0.44	0.26 (0.59, 0.37–0.93; P=0.024)	0.47	0.24 (0.51, 0.35–0.75; P<0.001)
Major bleeding	3.4	3.6 (P=0.58)	3.09	2.13 (0.69, 0.60–0.80; P<0.001)
Intracranial bleeding	0.7	0.5 (0.67, 0.47–0.93; P=0.02)	0.80	0.33 (0.42, 0.30–0.58; P<0.001)
Extracranial bleeding	–	–	–	–

NOA

New Oral Anticoagulants

	Rivaroxaban	Dabigatran	Apixaban
Administration	Oral qd	Oral qd	Oral bid
Half-life (h)	~6-12	~6-12	~6-12
Reversibility	No antidote available	No antidote available	No antidote available
Efficacy	Noninferior efficacy to current standard	Noninferior efficacy to current standard	Superior efficacy to current standard
Bleeding risk	Same incidence of bleeding as current standard	Same incidence of bleeding as current standard	Same incidence of bleeding as current standard
Liver enzyme elevation	Liver enzyme elevation with elevated bilirubin or symptomatic liver toxicity	Transient asymptomatic liver enzyme elevation	No liver enzyme elevation
Risk of HIT	Absence of HIT	Absence of HIT	Absence of HIT
Drug origin	Synthetic	Synthetic	Synthetic

HIT = heparin-induced thrombocytopenia.

Eikelboom and Weitz. *Circulation*. 2007;116:131.
Warfarin Institute of America. http://www.warfarinfo.com/rivaroxaban.htm. Accessed January 30, 2009.
Kwong. http://www.touchbriefings.com/download.cfm?fileID=10345. Accessed January 30, 2009.
Warfarin Institute of America. http://www.warfarinfo.com/dabigatran.htm. Accessed January 30, 2009.
Lassen et al. *J Thromb Haemost*. 2007;5:2368.

Dabigatran in elective surgery

Anticoagulation interruption for el

In the preoperative phase, pati
warfarin can be managed with or
anticoagulant therapy.[16] The reco
warfarin 5 days before the proce
risk for thromboembolism, low-m
or unfractionated heparin can be
patient. Postoperatively, resumpti
therapy was encouraged as soon
or without bridging therapy. Pati
dabigatran required discontinuati
apy at least 24 hours before the pr
of therapy, post procedure, as soo

duration of exposure, the required power of the primary comparison (type II error) and the significance level (type I error). Because there are 2 doses to be compared with warfarin, we adopted the Hochberg procedure[15] to account for multiple comparisons. Assuming a 2-year recruitment period and at least 1 year of follow-up and a primary event rate of 1.6% per year, it was determined that at least 15,000 patients would be needed to achieve a minimum of 450 events. The study would have approximately 84% power to conclude noninferiority of dabigatran over warfarin at α of .025 (1-sided) level.

Secondary outcomes include a composite of all stroke (including hemorrhagic), systemic embolism, and death as well as a composite of all stroke, systemic embolism, pulmonary embolism, acute myocardial infarction, and vascular death (including death from bleeding). The other end points include the individual occurrence of the components of the primary and secondary end points, as well as transient ischemic attacks (TIAs) and hospitalizations and a net clinical benefit as measured by the composite of stroke, systemic embolism, pulmonary embolism, acute myocardial infarction, all-cause death, and major bleeds (Appendix 3).

The identification of patient factors that determine bleeding and stroke risk will be an important aspect in determining the risk-benefit profile of both warfarin and dabigatran. In RE-LY, it is expected that patients who were previously treated with VKAs represent a selected population (survivor bias) and may differ in their efficacy and safety response compared with those who are VKA-naive. A subgroup analysis comparing dabigatran versus warfarin in these 2 groups of patients will be performed for the primary outcome and for major hemorrhage.

The safety of each dose of dabigatran will be compared with warfarin. The proportions of patients experiencing fatal or life-threatening bleeds, major bleeds, minor bleeds, or bleeds leading to permanent discontinuation will be determined for each treatment group (Appendix 3). The laboratory assessment of liver function will be closely followed up during the first year of exposure for all treatment groups.

To avoid bias, a prospective, blinded end point methodology was adopted. Outcomes are objective, clearly defined, and clinically relevant. The outcome events including strokes, non–central nervous system systemic emboli, deaths, myocardial infarctions, pulmonary embolism, major bleeds, and some minor bleeds are adjudicated by a blinded adjudication committee. The TIAs are also adjudicated to capture potential strokes. To ensure that all events are captured, there will be a review of all hospitalizations, events suggesting loss of neurologic function, or indicators of bleeding such as hemoglobin level decrease >2 g/dL. Furthermore, at every visit, a questionnaire to detect signs and symptoms of bleeding or stroke is administered to identify potential end points.

The trial is unblinded with respect to dabigatran or warfarin assignment. However, all investigators, members of the coordinating center, the operations committee, the steering committee, the event adjudication committee, and the sponsor remain blinded to treatment level analyses of efficacy and safety. Only the data and safety monitoring board (DSMB) and the DSMB-associated statistician have access to the randomization code and by-treatment event rates.

Study organization

The study organization is outlined in Appendix 4, available online.

Use of concomitant drugs

The trial allows acetylsalicylic acid (ASA) (≤100 mg/day), clopidogrel, ticlopidine, dipyridamole, or ASA/dipyridamole. The use of nonstudy warfarin or other VKAs is only permitted if patients are withdrawn from study medication. ASA-containing over-the-counter medications, long-term use of corticosteroids, nonsteroidal anti-inflammatory drugs or heparin, and fibrinolytic agents are discouraged.

P-glycoprotein inhibitors may interact with dabigatran. Quinidine doubles the concentration of dabigatran. The use of quinidine was not allowed in RE-LY as of the second quarter of 2008. The most common P-glycoprotein inhibitors in chronic use in the AF population are verapamil and amiodarone. The DSMB have not reported an elevated bleeding risk with their concurrent use with dabigatran.

Anticoagulation interruption for elective surgical procedure

In the preoperative phase, patients randomized to warfarin can be managed with or without bridging anticoagulant therapy.[16] The recommendation is to stop warfarin 5 days before the procedure. In patients at high risk for thromboembolism, low-molecular-weight heparin or unfractionated heparin can be used to bridge the patient. Postoperatively, resumption of anticoagulant therapy was encouraged as soon as clinically feasible with or without bridging therapy. Patients randomized to dabigatran required discontinuation of anticoagulant therapy at least 24 hours before the procedure and resumption of therapy, post procedure, as soon as clinically feasible.

Cardioversion

If there was a need for cardioversion (electric or pharmacologic) during the study, the protocol recommends that patients be maintained on the study drug (warfarin or dabigatran) unless, in the judgment of the investigator, another approach was deemed necessary. As a safety measure, transesophageal echocardiographs were encouraged but not mandated in patients assigned to dabigatran, who required cardioversion. If cardioversion was planned within 60 days of randomization, a transesophageal echocardiograph was recommended

Ezekowitz MD, et al. *Am Heart J* 2009;157:805-10.

Elective surgery and RIVAROXABAN

- *4.4 Avvertenze speciali e precauzioni di impiego*

Raccomandazioni posologiche prima e dopo procedure invasive e interventi chirurgici

Qualora siano necessari una procedura invasiva o un intervento chirurgico, il trattamento con Xarelto deve essere interrotto, se possibile e sulla base del giudizio clinico del medico, almeno 24 ore prima dell'intervento.

Se la procedura non può essere rimandata, l'aumentato rischio emorragico deve essere valutato in rapporto all'urgenza dell'intervento.

Il trattamento con Xarelto deve essere ripreso al più presto dopo la procedura invasiva o l'intervento chirurgico, non appena la situazione clinica lo consenta e sia stata raggiunta un'emostasi adeguata (vedere paragrafo 5.2).

Conclusions

- Mantain ASA-P2Y bl in the major part of ES
- Postpone after PCI/DES or BMS till is possible ES if HR of bleeding
- Stop P2Y bl after 6 m in non complicated PCI if bleeding HR
- Bridge Therapy (LMWH 100U/kg bid) only in IR and HR of bleeding surgery
- NOA will change horizon? No bridge thrp