DAPT E TERAPIA ANTICOAGULANTE:

triplice terapia post SCA

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DEFINIZIONI:

- **DUPLICE TERAPIA (DAPT):**

→ aspirina + inibitore del recettore piastrinico P2Y12 (clopidogrel, ticagrelor, prasugrel)

- **TRIPLICE TERAPIA:**

→ aspirina + inibitore del recettore piastrinico P2Y12 (clopidogrel, ticagrelor, prasugrel) + TAO/NAO

- **TERAPIA DUALE:**

→ singolo antiaggregante + TAO/NAO

Terapia antiaggregante
Quale e per quanto tempo

Sindrome coronarica acuta (angina instabile, NSTEMI, STEMI)

→ acido acetilsalicilico (75-100 mg/die)

\+

clopidogrel (75 mg/die)
ticagrelor (90 mg x 2/die)
prasugrel (10 mg/die)

} per 12 mesi

→ se elevato rischio di sanguinamento duplice terapia antiaggregante per soli 6 mesi

→ in casi selezionati duplice terapia antiaggregante > 12 mesi

Quali anticoagulanti?

- Antagonista vitamina K: warfarin

- Nuovi anticoagulanti diretti:
  - Dabigatran (150 mg x 2, 110 mg x 2)
  - Rivaroxaban (20 mg, 15 mg)
  - Apixaban (5 mg x 2, 2,5 mg x 2)
  - Edoxaban (60 mg, 30 mg)

Terapia antiaggregante e anticoagulante
Quale e per quanto tempo

Quando associare terapia antiaggregante e anticoagulante?

→ aumentato rischio di sanguinamento di 2-3 volte rispetto alla sola terapia anticoagulante

→ quando la sindrome coronarica acuta si associa a:

- fibrillazione atriale
- trombosi endoventricolare sinistra
- protesi valvolari cardiache meccaniche
- tromboembolismo venoso

→ la triplice terapia deve essere fatta per il minor tempo possibile valutando sia il rischio ischemico che il rischio emorragico

Terapia antiaggregante e anticoagulante
Quale e per quanto tempo

Perché associare terapia antiaggregante e anticoagulante?

→ aumentato rischio di sanguinamento

- La duplice terapia antiaggregante è necessaria per prevenire la trombosi dello stent, ma non sufficiente per la prevenzione dell'ictus e viceversa gli anticoagulanti orali sono essenziali per la prevenzione dell'ictus, ma non utili per prevenire nuovi eventi coronarici, soprattutto nella fase acuta e subacuta

Recommendations for stroke prevention in patients with atrial fibrillation

Recommendations	Class[a]	Level[b]	Ref[c]
Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA_2DS_2-VASc score of 2 or more.	I	A	38, 318–321, 354, 404
Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA_2DS_2-VASc score of 3 or more.	I	A	38, 318–321, 354, 404
Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA_2DS_2-VASc score of 1, considering individual characteristics and patient preferences.	IIa	B	371, 375–377
Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA_2DS_2-VASc score of 2, considering individual characteristics and patient preferences.	IIa	B	371, 376, 377
Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.	I	B	274, 435–440
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a vitamin K antagonist.	I	A	39, 318–321, 404
When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored.	I	A	395, 432, 441-444
AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contra-indications to NOAC (e.g. prosthetic valve).	IIb	A	39, 318, 319, 404, 408
Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition.	III (harm)	B	429, 445
In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention.	III (harm)	B	368, 371, 376, 377
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (harm)	A	38, 429, 430
NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C).	III (harm)	B C	318–321, 400, 404

Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial

*The ACTIVE Writing Group on behalf of the ACTIVE Investigators**

Summary

Background Oral anticoagulation therapy reduces risk of vascular events in patients with atrial fibrillation. However, long-term monitoring is necessary and many patients cannot achieve optimum anticoagulation. We assessed whether clopidogrel plus aspirin was non-inferior to oral anticoagulation therapy for prevention of vascular events.

Methods Patients were enrolled if they had atrial fibrillation plus one or more risk factor for stroke, and were randomly allocated to receive oral anticoagulation therapy (target international normalised ratio of 2·0–3·0; n=3371) or clopidogrel (75 mg per day) plus aspirin (75–100 mg per day recommended; n=3335). Outcome events were adjudicated by a blinded committee. Primary outcome was first occurrence of stroke, non-CNS systemic embolus, myocardial infarction, or vascular death. Analyses were by intention-to-treat. This study is registered with ClinicalTrials.gov, number NCT00243178.

Results The study was stopped early because of clear evidence of superiority of oral anticoagulation therapy. There were 165 primary events in patients on oral anticoagulation therapy (annual risk 3·93%) and 234 in those on clopidogrel plus aspirin (annual risk 5·60%; relative risk 1·44 (1·18–1.76; p=0.0003). Patients on oral anticoagulation therapy who were already receiving this treatment at study entry had a trend towards a greater reduction in vascular events (relative risk 1·50, 95% CI 1·19–1·80) and a significantly (p=0·03 for interaction) lower risk of major bleeding with oral anticoagulation therapy (1.30; 0.94–1.79) than patients not on this treatment at study entry (1·27, 0·85–1·89 and 0·59, 0·32–1·08, respectively).

Conclusion Oral anticoagulation therapy is superior to clopidogrel plus aspirin for prevention of vascular events in patients with atrial fibrillation at high risk of stroke, especially in those already taking oral anticoagulation therapy.

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See Comment page 1877

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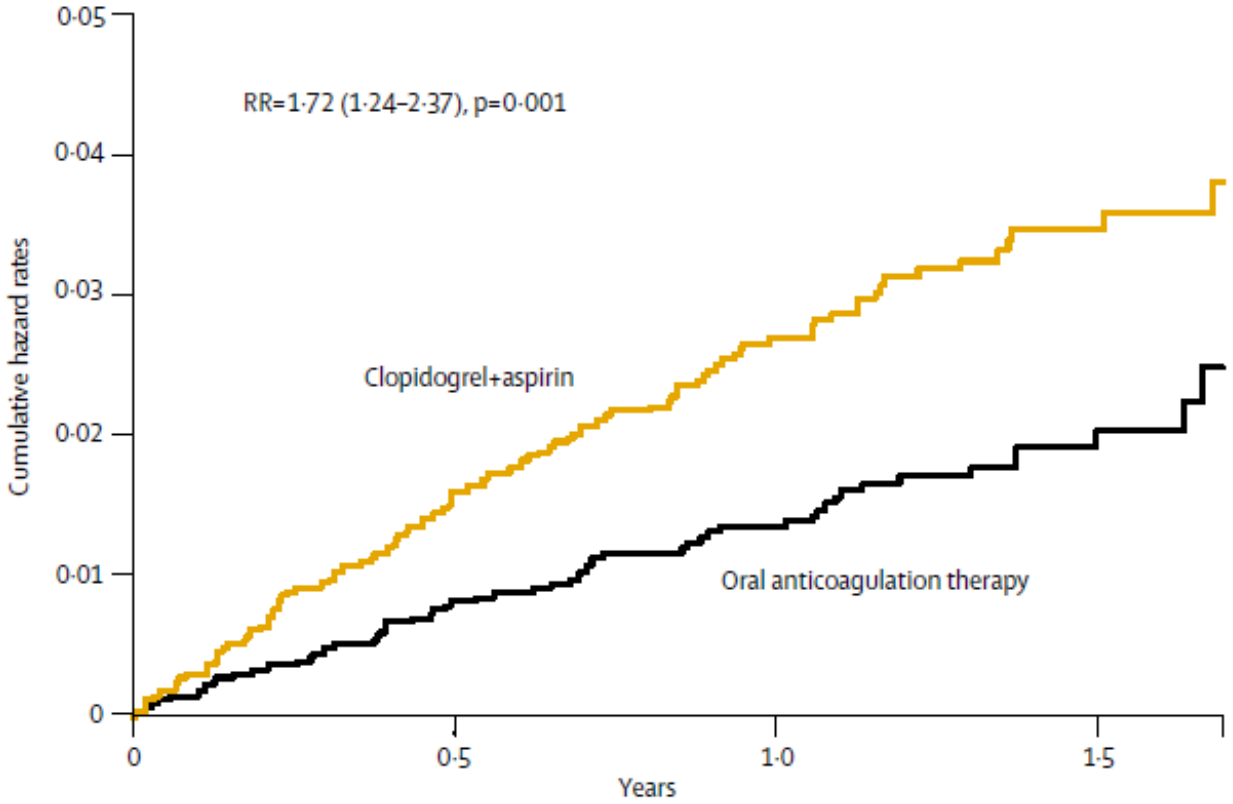

Number at risk

Clopidogrel +aspirin	3335	3168	2419	941
Oral anticoagulation therapy	3371	3232	2466	930

***Figure 3*: Cumulative risk of stroke**

	Clopidogrel+aspirin		Oral anticoagulation		Clopidogrel+aspirin *vs* oral anticoagulation	
	Number	Risk (% per year)	Number	Risk (% per year)	RR (95% CI)	p
Composite of stroke, non CNS embolus, myocardial infarction, vascular death	234	5·60	165	3·93	1·44 (1·18–1·76)	0·0003
Non-CNS embolus	18	0·43	4	0·10	4·66 (1·58–13·8)	0·005
Myocardial infarction	36	0·86	23	0·55	1·58 (0·94–2·67)	0·09
Stroke	100	2·39	59	1·40	1·72 (1·24–2·37)	0·001
Ischaemic	90	2·15	42	1·00	2·17 (1·51–3·13)	<0·0001
Haemorrhagic	5	0·12	15	0·36	0·34 (0·12–0·93)	0·036
Stroke severity						
Non-disabling	42	1·00	17	0·40	2·49 (1·42–4·37)	0·002
Disabling	58	1·39	40	0·95	1·47 (0·98–2·20)	0·06
Fatal	14	0·33	15	0·36	0·93 (0·45–1·94)	0·85
Total mortality	159	3·80	158	3·76	1·01 (0·81–1·26)	0·91
Vascular death	120	2·87	106	2·52	1·14 (0·88–1·48)	0·34
Non-vascular death	39	0·93	52	1·24	0·76 (0·50–1·15)	0·20
Haemorrhage						
Major (includes severe and fatal)	101	2·42	93	2·21	1·10 (0·83–1·45)	0·53
Severe	71	1·70	66	1·57	1·09 (0·78–1·52)	0·62
Fatal	7	0·17	11	0·26	0·64 (0·25–1·66)	0·36
Minor	568	13·58	481	11·45	1·23 (1·09–1·39)	0·0009
Total	644	15·40	555	13·21	1·21 (1·08–1·35)	0·001
Net benefit						
Primary outcome and major bleed	316	7·56	229	5·45	1·41 (1·19–1·67)	<0·0001
Primary outcome, major bleed, and death	348	8·32	271	6·45	1·31 (1·12–1·54)	0·0008

Table 2: **Primary and secondary outcomes**

Quale terapia antiaggregante associare all'anticoagulante?

Alla terapia anticoagulante con warfarin o con i nuovi anticoagulanti orali + acido acetilsalicilico si associa il **clopidogrel**

In assenza di studi clinici randomizzati e per l'aumentato rischio emorragico, l'uso di prasugrel o ticagrelor nella triplice terapia dovrebbe essere evitato

Quale terapia anticoagulante associare alla terapia antiaggregante?

Warfarin se:

- protesi meccaniche cardiache
- FA in stenosi mitralica moderato-severa
- primi 3 mesi dopo sostituzione valvolare con protesi biologica
- primi 3 mesi dopo valvuloplastica mitralica chirurgica
- protesi biologiche in sede mitralica in stenosi reumatica
- trombosi endoventricolare sinistra
- TEP

Nuovi anticoagulanti orali da preferire nella fibrillazione atriale "non valvolare"

Table 8 Strategies to avoid bleeding complications in oral anticoagulation patients

Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA_2DS_2-VASc, ABC, and HAS-BLED) with a focus on modifiable risk factors.
Keep triple therapy duration as short as possible; dual therapy after PCI (OAC and clopidogrel) to be considered instead of triple therapy.
One should consider the use of a NOAC instead of a VKA when NOACs are not contraindicated.
Consider a target INR in the lower part of the recommended target range and maximize time in the therapeutic range (i.e. >65%) when a VKA is used.
Clopidogrel is the $P2Y_{12}$ inhibitor of choice.
Use low-dose (≤100 mg daily) aspirin.
Routine use of PPIs.

Adapted from Valgimigli et al[410]

ABC = Age, Biomarkers, Clinical history; CHA2DS2-VASc = Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, prior Stroke or transient ischaemic attack or thromboembolism (doubled), Vascular disease, Age 65–74 years, Sex category (female); HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly; INR = international normalized ratio; NOAC = non-vitamin K antagonist OAC; OAC = oral anticoagulant; PPIs = proton pump inhibitors; VKA = vitamin K antagonist.

HAS-BLED score for bleeding risk on oral anticoagulation in atrial fibrillation

Letter	Clinical Characteristic	Score (if present)
H	Hypertension (systolic ≥ 160 mmHg) – on treatment	1
A	Abnormal renal function (Dialysis, transplant, Cr > 2.6 mg/dL or > 200 µmol/L)	1
A	Abnormal liver function (Cirrhosis or bilirubin >2xNormal or AST/ALT/AP >3xNormal)	1
S	Stroke in past	1
B	Prior major bleeding or predisposition to bleeding	1
L	Labile INRs (Unstable/high INRs, time in therapeutic range <60%)	1
E	Elderly – age ≥ 65 years	1
D	Drugs: Medication usage predisposing to bleeding (antiplatelet agents, NSAIDs)	1
D	Drugs: Concomitant alcohol intake (≥8 drinks/week)	1
	Total HAS-BLED Score	Maximum score = 9

The risk of major bleeding within 1 year in patients with AF enrolled in the Euro Heart Study

Risk	Score Range	Annual risk of bleeding (%)
Low	0	1.13
Moderate	1 – 2	1 – 2
High	3+	2 – 12

A score of 3 or more indicates increased one year bleed risk on anticoagulation sufficient to justify caution or more regular review. The risk is for intracranial bleed, bleed requiring hospitalization or a hemoglobin drop > 2 g/L or that needs transfusion.

Table 9 High-risk features for ischaemic events

Prior stent thrombosis on adequate antiplatelet therapy
Stenting of the last remaining patent coronary artery
Diffuse multivessel disease, especially in diabetic patients
Chronic kidney disease (i.e. creatinine clearance <60 mL/min)
At least three stents implanted
At least three lesions treated
Bifurcation with two stents implanted
Total stented length >60 mm
Treatment of a chronic total occlusion
History of STEMI

STEMI = ST-elevation myocardial infarction.

Table 6 **Unfavourable patient profile for a combination of oral anticoagulant and antiplatelet therapy**

• Short life expectancy
• Ongoing malignancy
• Poor expected adherence
• Poor mental status
• End stage renal failure
• Advanced age
• Prior major bleeding/prior haemorrhagic stroke
• Chronic alcohol abuse
• Anaemia
• Clinically significant bleeding on dual antithrombotic therapy

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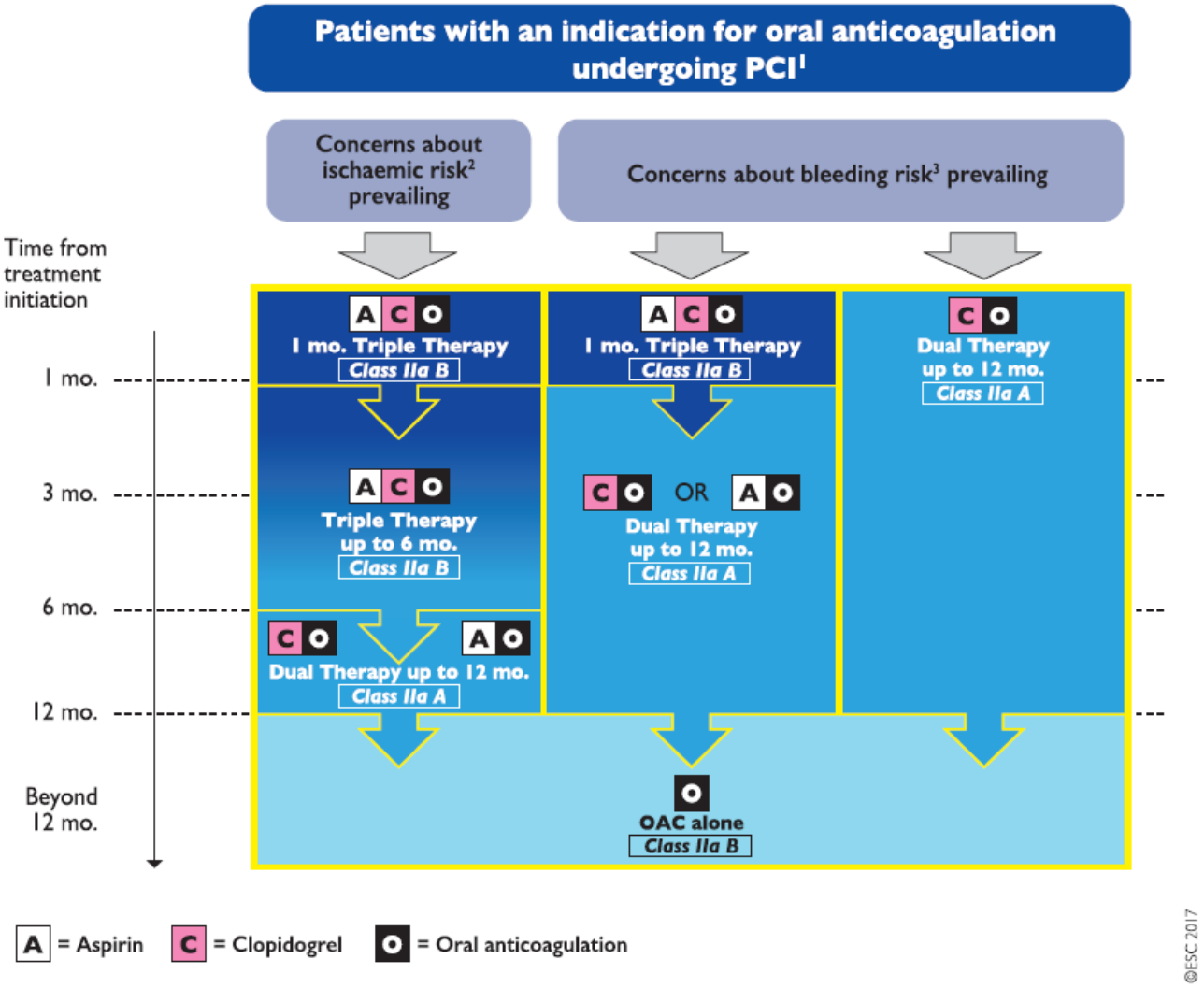
Recommendations for combination therapy with oral anticoagulants and antiplatelets

Recommendations	Class[a]	Level[b]	Ref[c]
After elective coronary stenting for stable coronary artery disease in AF patients at risk of stroke, combination triple therapy with aspirin, clopidogrel and an oral anticoagulant should be considered for 1 month to prevent recurrent coronary and cerebral ischaemic events.	IIa	B	522, 524
After an ACS with stent implantation in AF patients at risk of stroke, combination triple therapy with aspirin, clopidogrel and an oral anticoagulant should be considered for 1–6 months to prevent recurrent coronary and cerebral ischaemic events.	IIa	C	520
After an ACS without stent implantation in AF patients at risk of stroke, dual treatment with an oral anticoagulant and aspirin or clopidogrel should be considered for up to 12 months to prevent recurrent coronary and cerebral ischaemic events.	IIa	C	
The duration of combination antithrombotic therapy, especially triple therapy, should be kept to a limited period, balancing the estimated risk of recurrent coronary events and bleeding.	IIa	B	520
Dual therapy with any oral anticoagulant plus clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients.	IIb	C	524, 525

ACS = acute coronary syndromes; AF = atrial fibrillation; OAC = oral anticoagulant.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

LG ESC FA 2016

Terapia antiaggregante e anticoagulante
Per quanto tempo?



Terapia duale

Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

Willem J M Dewilde, Tom Oirbans, Freek W A Verheugt, Johannes C Kelder, Bart J G L De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias [illegible], Antonius A C M Heestermans, Marije M Vis, Jan G P Tijsen, Arnoud W van 't Hof, Jurriën M ten Berg, for the WOEST study investigators

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

C. Michael Gibson, M.D., Roxana Mehran, M.D., Christoph Bode, M.D., Jonathan Halperin, M.D., Freek W. Verheugt, M.D., Peter Wildgoose, Ph.D., Mary Birmingham, Pharm.D., Juliana Ianus, Ph.D., Paul Burton, M.D., Ph.D., Martin van Eickels, M.D., Serge Korjian, M.D., Yazan Daaboul, M.D., Gregory Y.H. Lip, M.D., Marc Cohen, M.D., Steen Husted, M.D., Eric D. Peterson, M.D., M.P.H., and Keith A. Fox, M.B., Ch.B.

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

Christopher P. Cannon, M.D., Deepak L. Bhatt, M.D., M.P.H., Jonas Oldgren, M.D., Ph.D., Gregory Y.H. Lip, M.D., Stephen G. Ellis, M.D., Takeshi Kimura, M.D., Michael Maeng, M.D., Ph.D., Bela Merkely, M.D., Uwe Zeymer, M.D., Savion Gropper, M.D., Ph.D., Matias Nordaby, M.D., Eva Kleine, M.Sc., Ruth Harper, Ph.D., Jenny Manassie, B.Med.Sc., James L. Januzzi, M.D., Jurrien M. ten Berg, M.D., Ph.D., P. Gabriel Steg, M.D., and Stefan H. Hohnloser, M.D., for the RE-DUAL PCI Steering Committee and Investigators*

Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation

Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial

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WOEST trial Lancet 2013
Clopidogrel + warfarin

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WOEST trial Lancet 2013
Clopidogrel + warfarin

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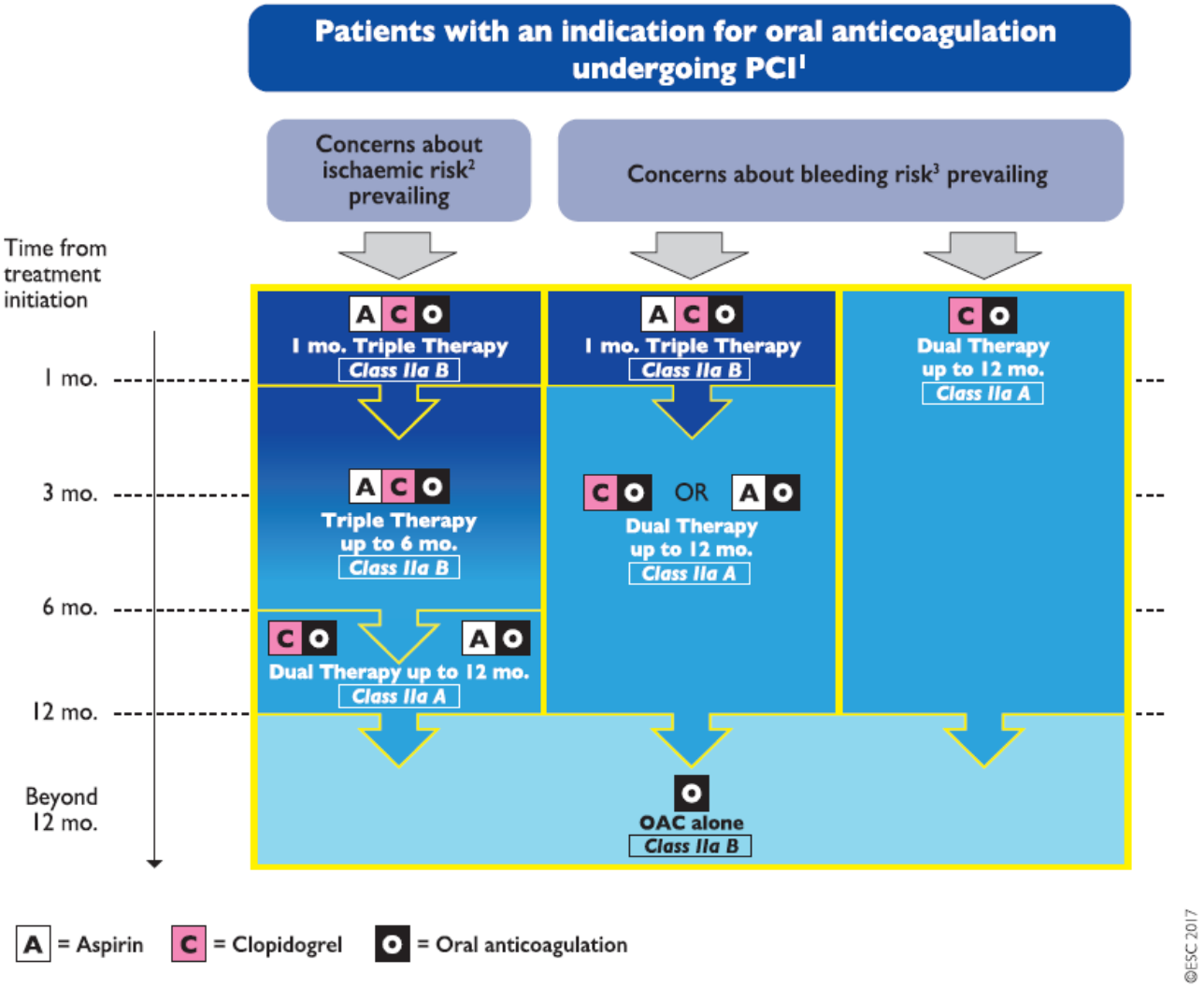
Terapia antiaggregante e anticoagulante
Per quanto tempo?



TAKE HOME MESSAGES

- la terapia antiaggregante e anticoagulante deve essere individualizzata in base alle caratteristiche del paziente (rischio ischemico vs rischio emorragico)
- triplice terapia per il minor tempo possibile
- possibile terapia duale (dalla dimissione)
- importanza della aderenza alla terapia per i NOAC
- monitoraggio:
  - → emocromo, funzione renale, funzione epatica
  - → se warfarin → INR tra 2.0 e 2.5