

Supplementary Tables to TH-09-08-0580 (Thromb Haemost 2009; 102.6):

“Management of Antithrombotic Therapy in Atrial Fibrillation Patients Presenting With Acute Coronary Syndrome and/or Undergoing Percutaneous Coronary Intervention/ Stenting: A Consensus Document of the European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association [EHRA] and the European Association of Percutaneous Cardiovascular Interventions [EAPCI]”

Suppl. Table 1: Recommendations in other recent guidelines (2006+).

Guideline	Ref	Recommendation
ACC/AHA/ESC guidelines for AF 2006	10	<p>Following percutaneous coronary intervention or revascularization surgery in patients with AF, low-dose aspirin (less than 100 mg per d) and/or clopidogrel (75 mg per d) may be given concurrently with anticoagulation to prevent myocardial ischemic events, but these strategies have not been thoroughly evaluated and are associated with an increased risk of bleeding. (Level of Evidence: C)</p> <p>In patients undergoing percutaneous coronary intervention, anticoagulation may be interrupted to prevent bleeding at the site of peripheral arterial puncture, but the vitamin K antagonist should be resumed as soon as possible after the procedure and the dose adjusted to achieve an INR in the therapeutic range. Aspirin may be given temporarily during the hiatus, but the maintenance regimen should then consist of the combination of clopidogrel, 75 mg daily, plus warfarin (INR 2.0 to 3.0). Clopidogrel should be given for a minimum of 1 mo after implantation of a bare metal stent, at least 3 mo for a sirolimus-eluting stent, at least 6 mo for a paclitaxel-eluting stent, and 12 mo or longer in selected patients, following which warfarin may be continued as monotherapy in the absence of a subsequent coronary event. When warfarin is given in combination with clopidogrel or low-dose aspirin, the dose intensity must be carefully regulated. (Level of Evidence: C)</p>
NICE guidelines for AF management 2006	11	<p>‘... the addition of aspirin to oral anticoagulation produced “no extra benefit for stroke prevention but increased bleeding risk” and recommended that for</p> <p>For stroke prevention in AF, aspirin should not be administered as adjunctive therapy to warfarin. It was considered a matter for clinical judgement on the appropriateness, duration, and safety (<i>eg</i>, risk of bleeding) of the concomitant administration of warfarin with aspirin, for example, in the setting of vascular disease, was considered a matter of clinical judgement.</p>
ESC PCI guidelines 2006	12	None
ESC NSTEMI guidelines 2007	8	<p>‘... treatment decisions continue to be made on an individualized basis and should include information on key factors, including bleeding and thrombo-embolic risks. On the basis of experiences from clinical practice, it seems that antiplatelet and OAC combinations lead to only modest increases in bleeding risk in elderly patients, provided tight control of INR can be obtained.</p>

		<p>In patients with active OAC treatment presenting with ACS, initiation of the anticoagulants recommended during the acute phase (UFH, LMWH, fondaparinux, or bivalirudin) should be withheld as long as the INR is not known, and not started before the INR is <2.0. Reversal of anticoagulation with vitamin K supplements is not recommended unless necessary for bleeding complications.</p> <p>The triple association of aspirin, clopidogrel, and a OAC should only be given if a compelling indication exists, in which case, the lowest efficacious INR and shortest duration for the triple association should be targeted (IIa-C)</p>
ACC/AHA 2007 NSTEMI guidelines	13	<p>An indication for warfarin (e.g., for atrial fibrillation, mechanical prosthetic valve, or left ventricular thrombus) in addition to ASA and clopidogrel, which are indicated for most high-risk patients, arises occasionally after UA/ NSTEMI.</p> <p>In the 2004 STEMI guidelines, a Class IIb, Level of Evidence: C recommendation was given for the use of warfarin (INR 2.0 to 3.0) in combination with ASA (75 to 162 mg) and clopidogrel (75 mg per d) for patients with a stent implanted and concomitant indications for anticoagulation.</p> <p>Similarly, the 2005 PCI guidelines (2) stated that warfarin in combination with clopidogrel and low-dose ASA should be used with great caution and only when INR is carefully regulated (2.0 to 3.0). Despite a limited amount of subsequent observational data, the evidence base remains small, which leaves this recommendation at the Class IIb, Level of Evidence: C.</p> <p>When triple-combination therapy is selected for clear indications and is based on clinical judgment that benefit will outweigh the incremental risk of bleeding, then therapy should be given for the minimum time and at the minimally effective doses necessary to achieve protection.</p>
ESC STEMI guidelines 2008	9	<p>Aspirin can be replaced by oral anticoagulants at the recommended international normalized ratio (INR) if there is an indication for oral anticoagulation (e.g. atrial fibrillation, LV thrombus, mechanical valves).</p> <p>In some patients, there is an indication for dual antiplatelet therapy and oral anticoagulation (e.g. stent placement and AF). In the absence of prospective randomized studies, no firm recommendations can be given. Triple therapy seems to have an acceptable risk–benefit ratio provided clopidogrel co-therapy is kept short and the bleeding risk is low. Oral anticoagulants plus a short course of clopidogrel might be an alternative in patients with a higher risk of bleeding. Most importantly, drug-eluting stents should be avoided in patients who need oral anticoagulation.</p>
American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Primary and Secondary Prevention of Coronary Artery Disease 2008	14	<p>For high-risk patients with MI, including those with a large anterior MI, those with significant heart failure, those with intracardiac thrombus visible on transthoracic echocardiography, those with atrial fibrillation and those with a history of a thromboembolic event, we suggest the combined use of moderate-intensity (INR, 2.0 to 3.0) oral OAC plus low-dose aspirin (< 100 mg/d) for at least 3 months after the MI (Grade 2A).</p> <p>For patients undergoing stent placement with a strong concomitant indication for OAC, we suggest triple antithrombotic therapy (Grade 2C). We suggest 4 weeks of clopidogrel following BMS and 1 year following DES (Grade 2C).</p>

Suppl. Table 2: Applied classification of recommendations and level of evidence.

Classification of recommendations

Class I: Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful, and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy.

- Class IIa: Weight of evidence/opinion is in favour of usefulness/efficacy.
- Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful or effective and in some cases may be harmful.

Level of evidence

The weight of evidence was ranked from highest (A) to lowest (C), as follows:

Level of evidence A: Data derived from multiple randomized clinical trials or meta-analyses.

Level of evidence B: Data derived from a single randomized trial or nonrandomized studies.

Level of evidence C: Only consensus opinion of experts, case studies, or standard-of-care.

Suppl. Table 3(a): Details of individual studies, in relation to percutaneous coronary intervention performed.

First author	Ref	Publication year	n	Study Design	Outcome comparisons	ACS	Radial access (%)	Closure device (%)	GPI inhibitor (%)	Stent (%)	DES(%)
Rubboli	145	130	27	retrospective, single center	bleeding, TE, MACE	67%	0%	100%	30%	100%	0%
Orford	124	2004	66	retrospective, single center	bleeding, MACE	27%	14%		47%	97%	0%
Mattichak	147	2005	82	retrospective, single center	bleeding, stroke, MACE	100%			2%	100%	0%
Khurram	123	2006	107	retrospective, single center	bleeding					100%	
Lip	126	2006	35	retrospective, single center	bleeding	94%			74%	100%	14%
Porter	129	2006	180	retrospective, single center	bleeding	83%			48%		?
Rubboli	101	2007	49	retrospective, single center	bleeding, TE, MACE	28%	5%	44%	20%	73%	2%
Karjalainen	60	2007	239	retrospective, multicenter	bleeding, stroke, MACE	53%	21%	26%	28%	50%	42%
Rogacka	128	2007	127	retrospective, two-center	bleeding, MACE, stroke, stent thrombosis	50%				100%	56%
Nguyen (GRACE)	99	2007	800	prospective (post hoc), multicenter	bleeding, MACE, stroke, MI	77%			58%	100%	16%

DeEugenio	131	2007	97	retrospective, single center	bleeding				43%	100%	25%
Ruiz-Nodar	59	2008	426	retrospective, two-center	bleeding, TE, MACE	84%			26%	100%	40%
Manzano-Fernandez	83	2008	104	retrospective, single center	bleeding, MACE	96%	27%		38%	96%	66%
Wang	58	2008	1247	prospective (post hoc), multicenter	bleeding, transfusion, MI, heart failure						77%
Maegdefessel	125	2008	159	retrospective, single center	bleeding, stroke, MI, cardiovascular death	86%					
Rossini	127	2008	102	retrospective, two-center	bleeding, MACE	78%	32%	14%	47%	94%	47%
Karjalainen	72	2008	523	retrospective, multicenter	bleeding, MACE and access site complications	50%	21%	30%	27%		41%
Sarafoff	111	2008	515	prospective, two-center	bleeding, MACE, stroke, MI, death	33%				100%	100%
Ruiz Nodar	100	2009	604	retrospective, multicenter	bleeding, TE, MACE	85%			20%	100%	54%
Manzano-Fernandez	130	2009	166	retrospective, single center	bleeding, MACE	90%	22%		38%	100%	64%

ACS: acute coronary syndrome; DES: Drug Eluting Stent; TE thromboembolism; MACE major adverse cardiovascular events (usually a composite of death, myocardial infarction, stroke, and/or repeated revascularization)

Suppl. Table 3(b): Risk factor of patients included in individual studies.

First author	Ref	age (yrs)	AF (%)	Prior stroke (%)	Diabetes (%)	Hypertension (%)	Heart Failure (%)	Prior relevant bleed (%)	CRF (%)	<u>Comments</u>
Rubboli	145	67	52%		4%					Antithrombotic therapy in these patients showed substantial variability. Complication rate is relevant
Orford	124	74	39%							The risk of bleeding may be increased in patients treated with aspirin, a thienopyridine, and warfarin early after PCI with stent placement
Mattichak	146	63	43%	11%		62%		21%		Warfarin anticoagulation, in combination with successful coronary stenting for acute MI and antiplatelet therapy, does not reduce risk of reinfarction but is associated with increased rates of transfusion
Khurram	123	69	80%	6%	31%	82%				Triple therapy showed increased major bleeding
Lip	126	71	100%		34%	66%				Antithrombotic therapy in these patients showed substantial variability
Porter	129	65	37%		34%	51%				Short term triple therapy after PCI was not associated with prohibitively high bleeding complication rates
Rubboli	98	69	51%				14%			Antithrombotic therapy in these patients showed substantial variability
Karjalainen	60	70	70%	21%	30%	67%	24%			The prognosis is unsatisfactory in warfarin-treated patients irrespective of the drug combination used. Aspirin plus warfarin combination seems to be inadequate to prevent stent thrombosis

Rogacka	128	70	59%		24%	70%					Triple therapy is associated with increased major bleeding, one-half of the events are lethal, and most occurred with the first month
Nguyen (GRACE)	99	65	23%		22%	58%	11%				There were no differences in mortality or MI between triple therapy or one antiplatelet plus warfarin
DeEugenio1	131	70	60%		32%	66%		7%	6%		Warfarin use was an independent predictor of major bleeding after PCI in patients receiving dual antiplatelet therapy
Ruiz-Nodar	59	72	100%	16%	40%	75%	27%		15%		Patients with AF undergoing PCI with stenting represent a high-risk population. These patients have a high mortality and MACE rate, which is reduced by anticoagulation therapy.
Manzano-Fernandez	83	72	100%	24%	52%	82%	42%	14%	59%		A high rate of major bleeding is observed under triple therapy. GpIIb-IIIa inhibitor use, three or left main disease, triple therapy and anemia are predictor for bleeding
Wang	58	76	NR								Antithrombotic therapy in these patients showed substantial variability
Maegdefessel	125	70	100%	12%	29%	87%					No antithrombotic regimen seemed to be clearly superior in this setting
Rossini	127	68	67%	15%	23%	51%		0%	14%		In patients on triple therapy, targeting lower therapeutic INR values reduces the risk of bleeding
Karjalainen	72	69	72%	22%	29%	70%	22%				PCI is a safe procedure during uninterrupted oral anticoagulation with no excess bleeding complication
Sarafoff	111	71	78%		27%	89%					A double antiplatelet therapy and triple therapy are associated with favourable safety and efficacy

Ruiz Nodar	100	72	100%	16%	44%	77%	31%	27%	A higher risk of major bleeding with DES in comparison with BMS raises the possibility that DES should be limited to lesions or patients with a high risk of restenosis	
Manzano-Fernandez	130	71	63%	18%	53%	65%	35%	12%	50%	Chronic kidney disease is independently associated with increased major bleeding and all cause mortality after PCI

NR, not reported; CRF chronic renal failure; other abbreviations as Table w3(a)