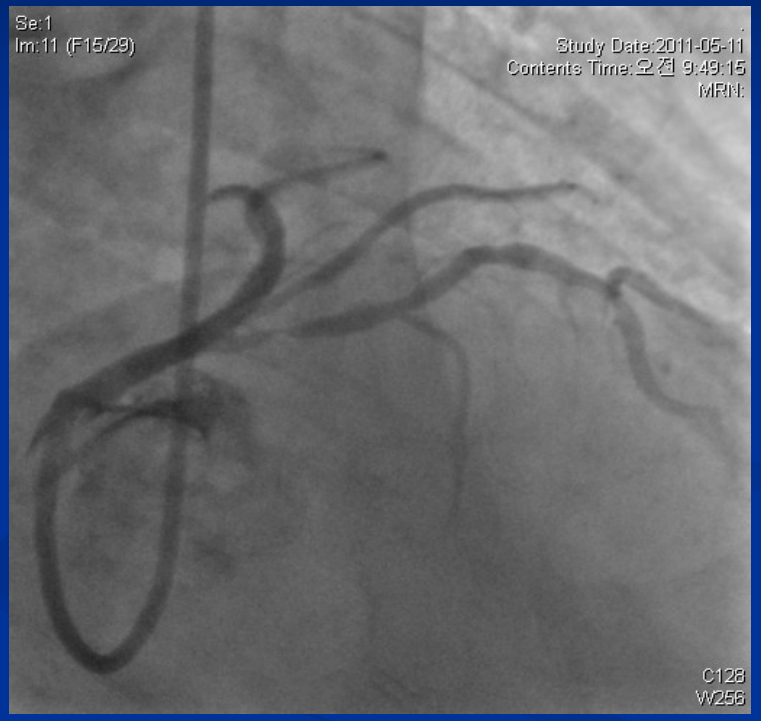
Management of Patients with Atrial Fibrillation Undergoing Coronary Artery Stenting

경북대 의전원 내과 조용근

Case (2011, 5)

- 74-years old gentleman
- Exertional chest pain
- Warfarin with good INR control
- Ex-smoker, social(?) – drinker
- Past history
  - Small lacunar infarction, left (2009, 10)
  - Reflux esophagitis (2008, 04)
  - AF, EF 40-45% (2005, 11)
  - HTN, DM (2000, 03)



허혈성심질환 표준진료 권고안 (2010)

항혈소제/항응고제: Clopidogrel			
아스피린이 금기인 경우 75 mg의 clopidogrel이나 와파린을 고려한다.	1. DES를 삽입한 PCI 후 모든 환자는 출혈의 위험이 크지 않으면 12개월간 매일 clopidogrel 75 mg을 복용해야 한다. BMS를 삽입한 환자는 최소 1개월은 복용해야 하며 이상적으로는 12개월간 복용한다(출혈의 위험이 높은 경우 최소 2주간은 복용).	I(A)	수정된 권고안 (텍스트 변경)
	2. 스텐트를 삽입하지 않은 모든 STEMI 환자(약물치료만 하거나 stenting 없이 PTCA)는 clopidogrel을 최소한 14일 이상 유지한다.	I(B)	새로운 권고안
	3. Clopidogrel을(하루에 75 mg) 장기간 투여(1년간)하는 것은 STEMI 환자에서 혈전용해제로 재관류를 하였든 재관류 치료를 하지 않았든 합리적이다.	IIa(C)	새로운 권고안
항혈소제/항응고제: Warfarin			
임상적으로 적응이 되거나 aspirin, clopidogrel 을 복용할 수 없는 경우 STEMI 후 환자에서 INR 2.5-3.5로 와파린 치료를 한다	1. 발작성 심방 세동이나 만성 심방세동, 심방 조동환자, 임상적으로 적응증(심방 세동, 좌심실 혈전)이 되는 심근 경색 후 환자는 INR 2.0-3.0으로 와파린 치료를 하는 것이 권장된다.	I(A)	수정된 권고안 (텍스트 변경)
	2. 아스피린/clopidogrel과 와파린을 병합 투여하는 경우 출혈 위험이 높아지므로 면밀하게 관찰하여야 한다.	I(B)	새로운 권고안
	3. 와파린, clopidogrel, 아스피린이 모두 필요한 환자는 저용량의 아스피린과 75 mg의 clopidogrel과 함께 INR 2.0-2.5로 유지하는 것이 권장된다.	I(C)	새로운 권고안
레닌-안지오텐신-알도스테론계 차단제: ACE inhibitor			
ACE 길항제는 모든 환자에서 지속적으로 사용한다; 안정형 고위험군에서 조기에 투여(전벽심근경색증, 과거의 심근경색증 병력, Killip Class가 II 이상 [S3 gallop, 수포음, 방사선학적 울혈성 심부전], 좌심실 구	1. ACE 길항제는 STEMI에서 회복된 환자 중 좌심실 구출율이 40% 이하이거나 고혈압, 당뇨, 만성 신질환이 있는 모든 환자에서 금기가 아니면 사용하여야 하고 지속적으로 투여하여야 한다.	I(A)	수정된 권고안 (텍스트 변경)
	2. ACE 길항제는 STEMI에서 회복된 환자 중 저 위험군(정상 심실기능을 가진 사람 중에 심혈관 위험요소가 잘 조절되고 혈관재관류술이 시행된	I(B)	새로운 권고안

는 아스피린을 162에서 325 mg 일일 용량으로 최소 1달 동안 매일 투여해야 한다(Level of Evidence: B). 이후 아스피린을 75 mg에서 162 mg 일일 용량으로 평생 투여해야 한다(Level of Evidence: B); clopidogrel 75 mg 일일 용량으로 최소한 한 달(Level of Evidence: A), 이상적으로 1년까지 투여되어야 한다(출혈위험이 증가되어 있을 경우 최소 2주간 투여되어야 한다).

3. 약물 용출 스텐트를 삽입 받은 불안정성 협심증/비ST분절상승 심근경색증 환자는 아스피린을 162에서 325 mg 일일 용량으로 sirolimus 용출 스텐트 삽입 시 최소 3개월 동안 paclitaxel 용출 스텐트 삽입 시 최소 6개월 동안 매일 투여 후 75 mg에서 162 mg 일일 용량으로 평생 투여해야 한다(Level of Evidence: B). 약물 용출 스텐트를 삽입 받은 모든 환자에서 clopidogrel 75 mg 일일 용량은 최소 12개월 이상 투여되어야 한다(Level of Evidence: B).
4. 불안정성 협심증/비ST분절 상승 심근경색증에서 회복중인 환자 중 아스피린 금기증이 있거나 과민반응 또는 소화기 장애로 아스피린을 복용하지 못하는 경우 우선 clopidogrel(경구로 매일 75 mg)로, 또는 ticlopidine(금기증이 없는 경우)으로 대치하는 것이 좋다(Level of evidence: A).

〈CLASS IIa〉

임상의가 출혈에 대하여 염려하고 있는 불안정성 협심증/비ST분절상승 심근경색증환자는 경피적 관동맥 중재술 후 저용량 아스피린으로 시작하는 것이 (100 mg에서 200 mg) 합당하다(Level of Evidence: C).

〈CLASS IIb〉

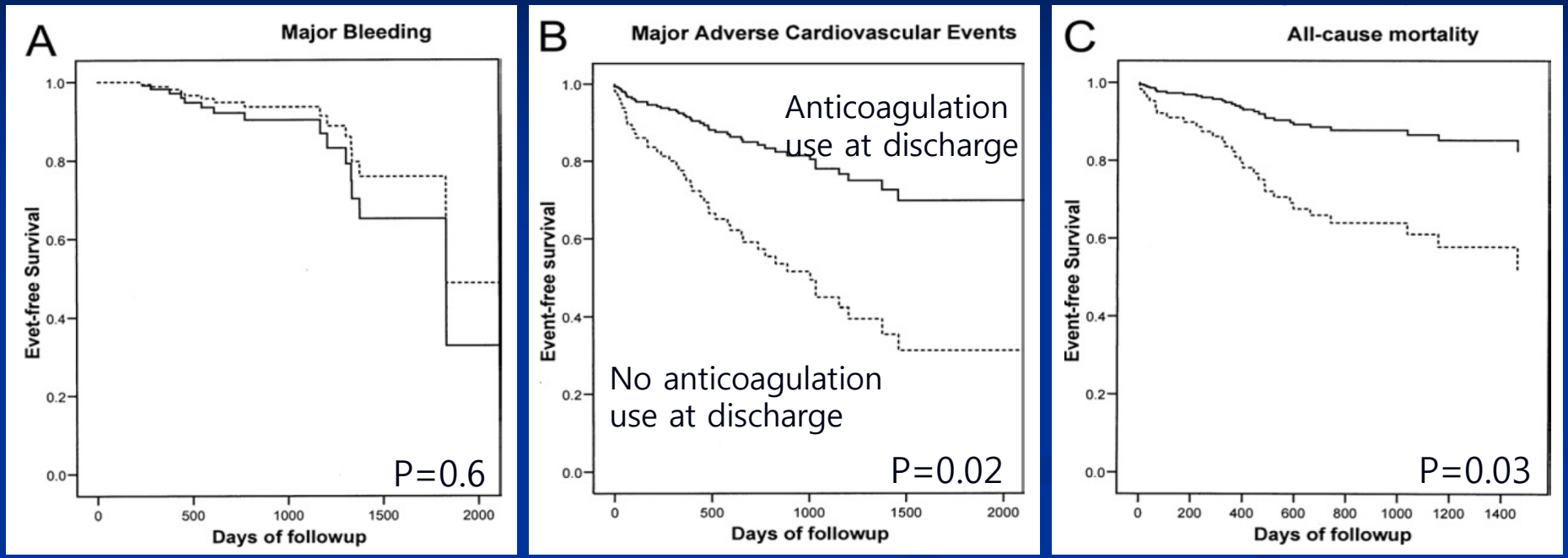
항응고 치료의 적응증이 되는 불안정성 협심증/비ST분절상승 심근경색증 환자에게는 INR 2.0에서 3.0 사이[F]로 유지하기 위해 와파린[R]을 추가한다(Level of Evidence: B).

〈CLASS III〉

Dipyridamole은 효과가 입증되지 않아 불안정성 협심증/비ST분절상승 심근경색증 후 환자에서 항혈소판제로 추천되지 않는다.

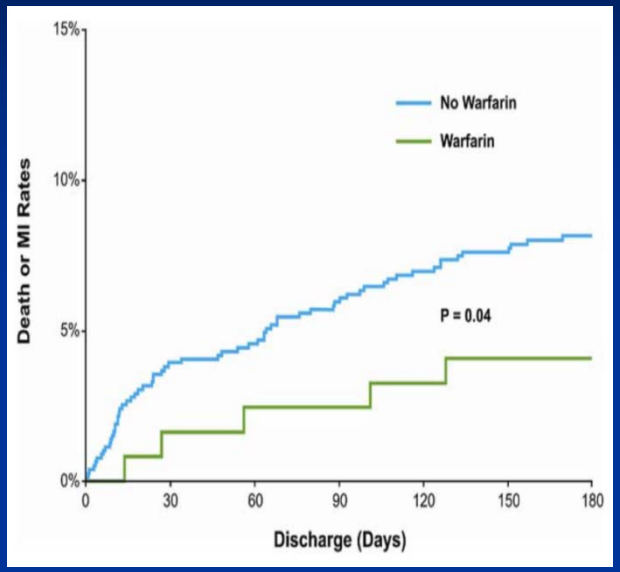
F: 아스피린은 영구적으로 사용하고 와파린은 다음과 같이 적응증이 될 경우 장기간 사용한다: 심방세동, 좌심실 내 혈전, 뇌혈관, 정맥 또는 폐동맥 색전증.
R: 아스피린과 clopidogrel이 투여되고 있는 동안, 특히 다른 출혈의 위험이 있는 노인 환자의 경우, international normalized ratio를 2.0에서 2.5 사이로 유지하는 것이 선호된다.

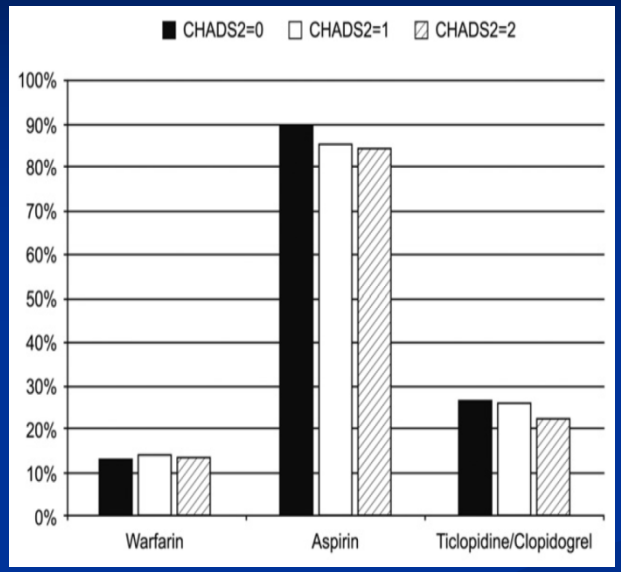
Anticoagulant and antiplatelet therapy use in patients with AF undergoing PCI-S

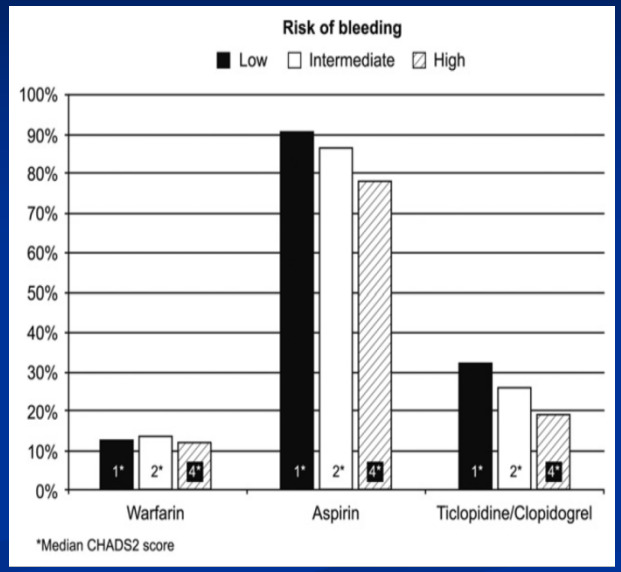


- N=426 (71% men, 72±8 years, permanent AF 60%, paroxysmal AF 40%, HTN 75%, DM 40%, HF or LV dysfunction 47%, CRF 15%). DES 40%. Triple therapy 50%., dual therapy 41%, single therapy 4%, single + warfarin 6%.
- Median FU = 1.6 year. Major bleeding 12.3%, thromboembolic event 4.2%, MACE (death, AMI, revascularization) 32.4%, all cause mortality 22.6%.
- Patients with AF undergoing PCI-S represent a high-risk population because of age, comorbidities, and presence of stroke risk factors. These patients have a high mortality and MACE rate, which is reduced by anticoagulation therapy. (Ruiz-Nodar et al. J Am Coll Cardiol 2008;51:818–25)

Warfarin use and outcomes in patients with AF complicating ACSs

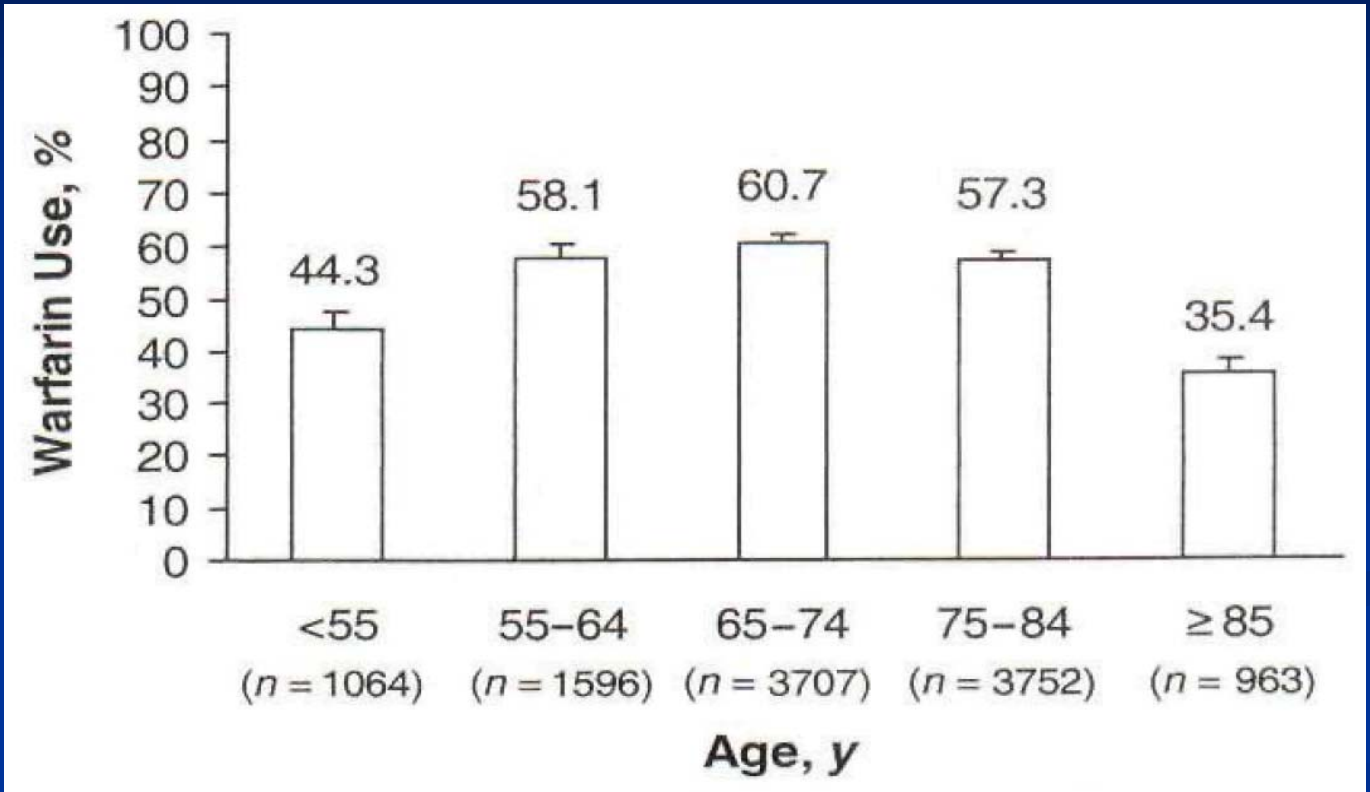






- Examined warfarin use at discharge and its association with 6-month death or MI in patients with post-ACS AF.
- N=23,208. 4.0% had AF and were discharged alive.
- Only 13.5% of patients with an ACS complicated by AF received warfarin at discharge.
- Warfarin is associated with better 6- month outcomes among patients with AF complicating an ACS, but its use is not related to $CHADS_2$ scores or bleeding risk.
- Among the components of the $CHADS_2$ score, the only significant predictor of warfarin use at discharge was heart failure (Lopes et al. Am J Med 2010;123:134-140).

Warfarin use by age in patients with nonvalvular AF and no identified contraindications to warfarin therapy



- 72±12 years. Male 57%. Previous stroke 9%, HTN 51%. CHF 31%. DM 17%. CAD 29%.
- Under-use of warfarin is greatest in elderly patients who are at the highest risk of stroke. Go A et al. Ann Intern Med 1999;131:927–34

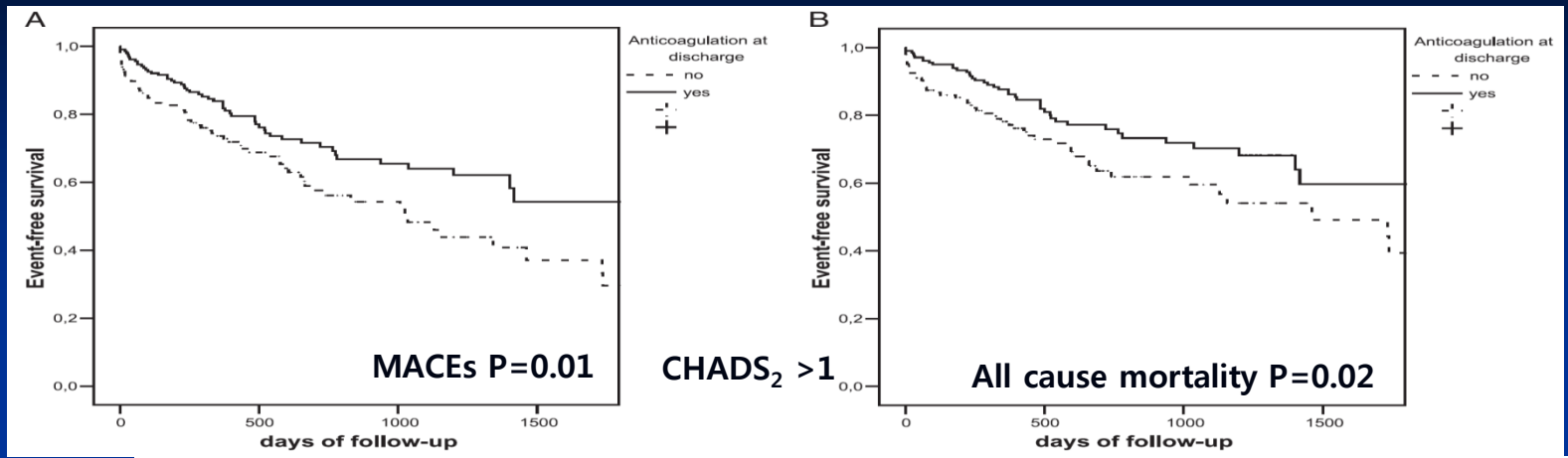
$CHADS_2$ score versus CHA_2DS_2-VASc score

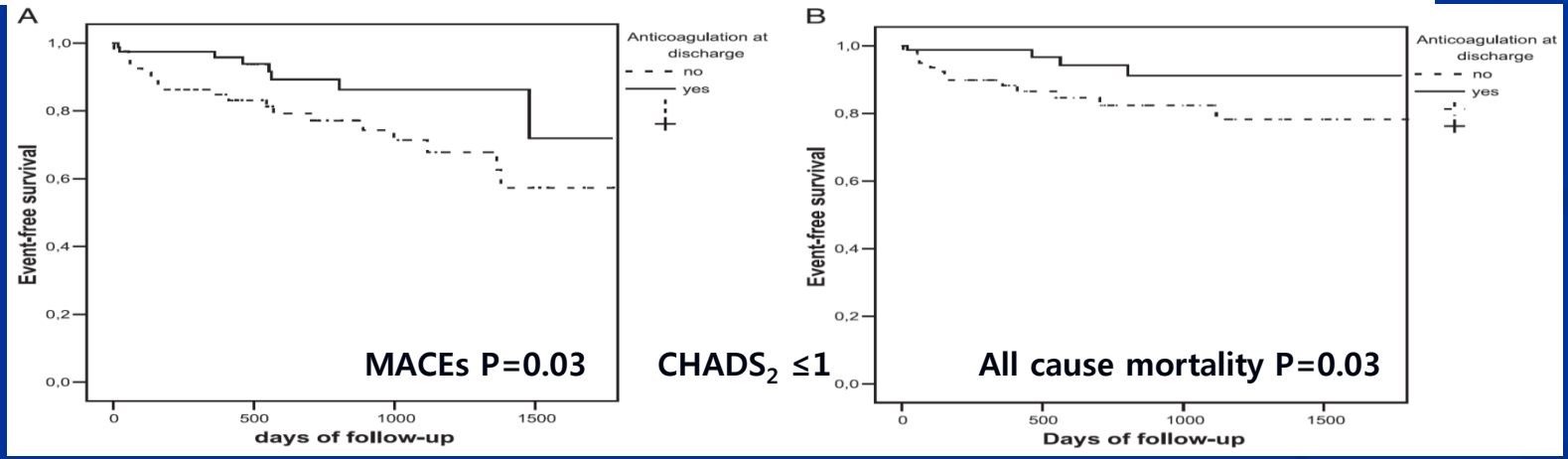
$CHADS_2$ score	6
CHF	1
Hypertension	1
Age >75	1
DM	1
Stroke/TIA	2
$CHADS_2$ score ≥2	OAC
$CHADS_2$ score = 1	OAC = ASA

CHA_2DS_2-VASc score	9
CHF	1
Hypertension	1
Age >75	2
DM	1
Stroke/TIA	2
Vascular disease	1
Age 65-75	1
Female sex	1
CHA_2DS_2-VASc score ≥2	OAC
CHA_2DS_2-VASc score =1	OAC ≥ASA

Camm et al. Eur Heart J 2010;31:2369-429

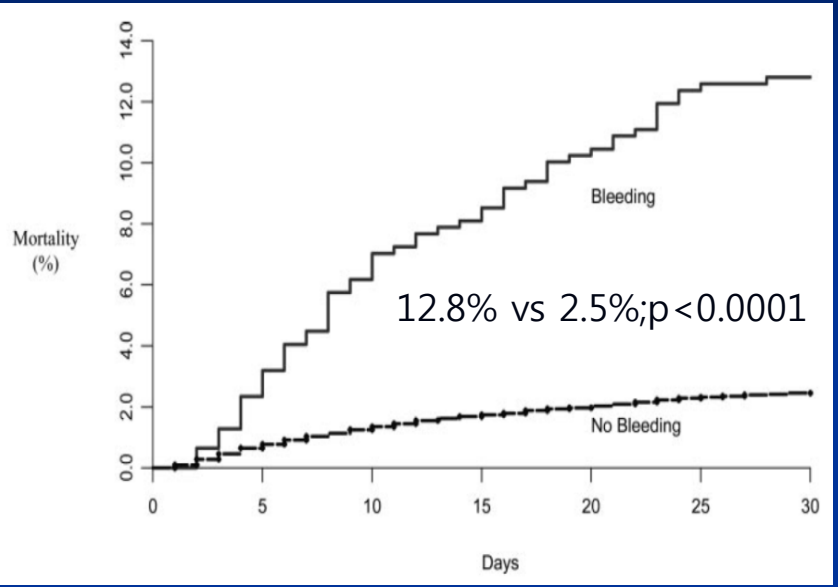
An evaluation of the $CHADS_2$ score in patients with AF who undergo PCI-S

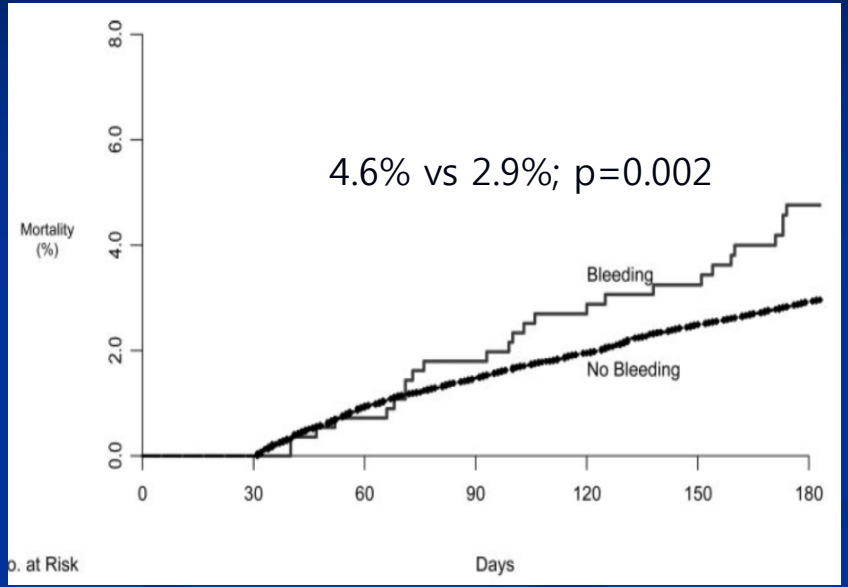




- N=604. (72% men, 72±8 years, HTN 77%, DM 43%, HF 31%, CRF 27%). DES 46%.
- Major bleeding 12%, thromboembolic event 5%, MACE 29%, all cause mortality 22% at 2 years.
- In patients with AF and PCI-S, even those with $CHADS_2$ ≤1 should be regarded as being at high risk. OAC should be considered as thromboprophylaxis in patients with AF and PCI-S. Ruiz-Nodar et al. Chest 2011;139:1402-9.

Adverse impact of bleeding on prognosis in patients with ACSs





- N=34,146. Major bleeding 2.0% during the first 6 months.
- Patients with major bleeding were older, more often had diabetes or a history of stroke, had a lower BP and higher serum creatinine, more often had ST-segment changes on the presenting ECG, and had higher incidence of death.
- In ACS patients, there is a strong and consistent association between bleeding and death. These data should lead to greater awareness of the prognostic importance of bleeding in ACS and should prompt evaluation of strategies to reduce bleeding and thereby improve clinical outcomes. (Eikelboom et al. Circulation 2006;114:774-782.)

Factors associated with an increased risk for stroke/thromboembolism and an increased risk of bleeding in AF patients

Risk factors for thromboembolism	Bleeding risk factors
Previous stroke, transient ischaemic attack, or embolism	Cerebrovascular disease
Age ≥75 years	Advanced age (>75 years)
(Age 65–74 years)	Age >85 years
Heart failure or moderate–severe LV dysfunction on echocardiography (e.g. EF ≤40%)	History of myocardial infarction or ischaemic heart disease
(Vascular disease)	
Hypertension	Uncontrolled hypertension
Diabetes mellitus	(Female gender)
(Female gender)	(Low body weight)
Mitral stenosis	
Prosthetic heart valve	
	Anaemia
Renal dysfunction (stage III–V)	[Renal dysfunction (stage III–V)]
	History of bleeding
	Concomitant use of other antithrombotic substances such as anti-platelet agents

Note that most factors pose patients at risk for both types of events. In AF patients in general, thrombo-embolic events (strokes) are approximately one magnitude more likely than severe bleeds. Less validated factors given in parentheses. 'Vascular disease' refers to myocardial infarction, complex aortic plaque, carotid disease, peripheral artery disease, and similar manifestations of arteriosclerosis. Europace 2009;11:860-85, Eur Heart J 2010;31:1311-8

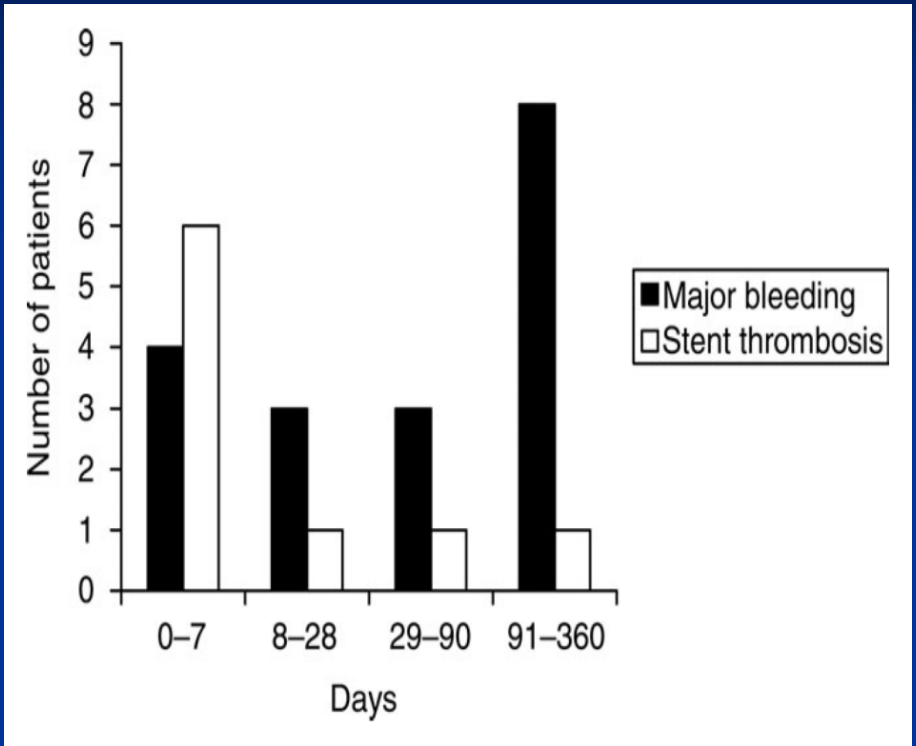
HAS-BLED bleeding risk score

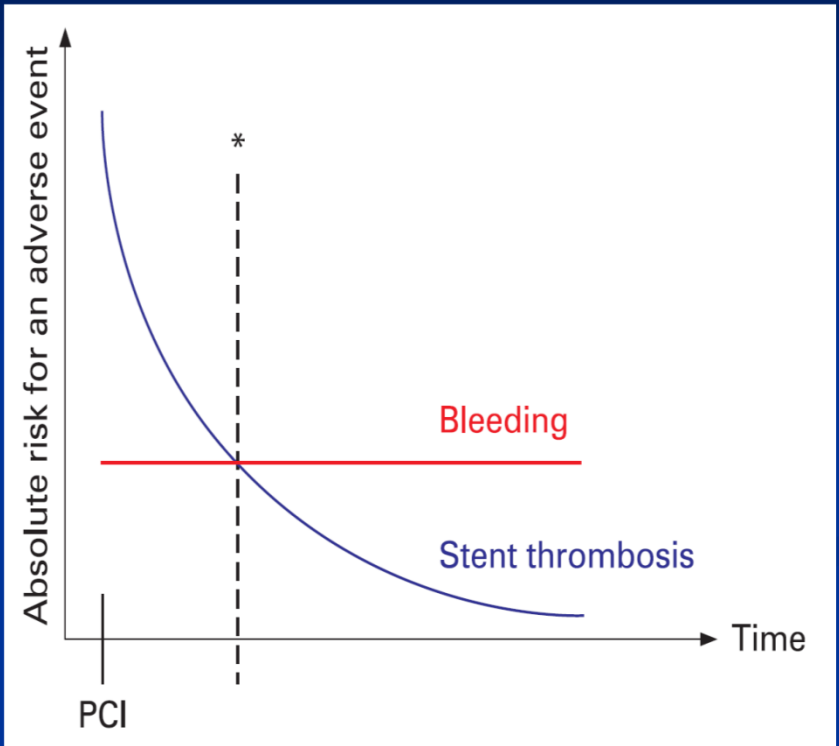
Letter	Clinical characteristics	Maximum 9 points
H	Hypertension	1
A	Abnormal renal or liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
	High-risk of bleeding	≥3

Pister et al. Chest 2010;138:1093-100, Camm et al. Eur Heart J 2010;31:2369-429

Safety and efficacy of combined antiplatelet-warfarin therapy after PCI-S

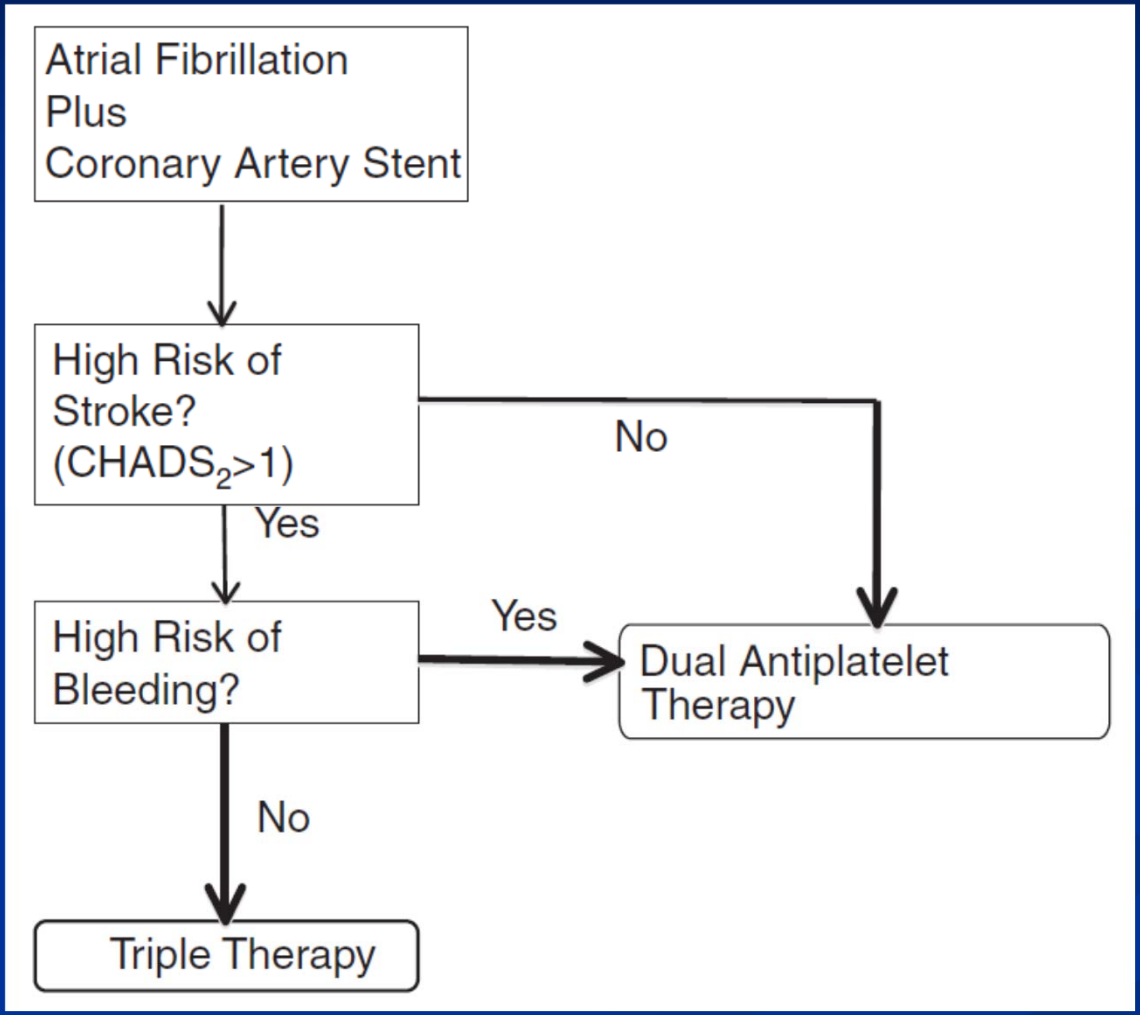
Timing of major bleeding events and stent thrombosis during follow-up





- N=239 (704 men, 70±9 years). DM 30%. HTN 67%. HF 24%. Stroke 21%. DES 42%.
- TAT 48%. DAT 16%. Warfarin+aspirin 15%. Warfarin+clopidogrel 21%.
- The bleeding risk of patients on triple therapy is grossly time independent, while the risk for stent thrombosis diminishes clearly over time. Karjalainen et al. European Heart J 2007;28:726-32.

Decision algorithm for antithrombotic therapy in patients with AF and a coronary artery stent



Paikin et al. Circulation 2010;121:2067-70

Recommended antithrombotic strategies following PCI-S in patients with AF at moderate-to-high thromboembolic risk in whom oral anticoagulation therapy is required (2010 EHRA-EAPCI Consensus, Lip et al. Eur Heart J 2010;31:1311-8)

Haemorrhagic risk	Clinical setting	Stent implanted	Recommendations
Low or intermediate	Elective	Bare metal	1 month: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day
			Lifelong: warfarin (INR 2.0–3.0) alone
	Elective	Drug eluting	3 (-olimus group) to 6 (paclitaxel) months: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day
			Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin 100 mg/day)[a]
			Lifelong: warfarin (INR 2.0–3.0) alone
	ACS	Bare metal/drug eluting	6 months: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day
			Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin 100 mg/day)[a]
			Lifelong: warfarin (INR 2.0–3.0) alone
High	Elective	Bare metal[b]	2–4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day
			Lifelong: warfarin (INR 2.0–3.0) alone
	ACS	Bare metal[b]	4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day
			Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin 100 mg/day); mg/day);[a]
			Lifelong: warfarin (INR 2.0–3.0) alone

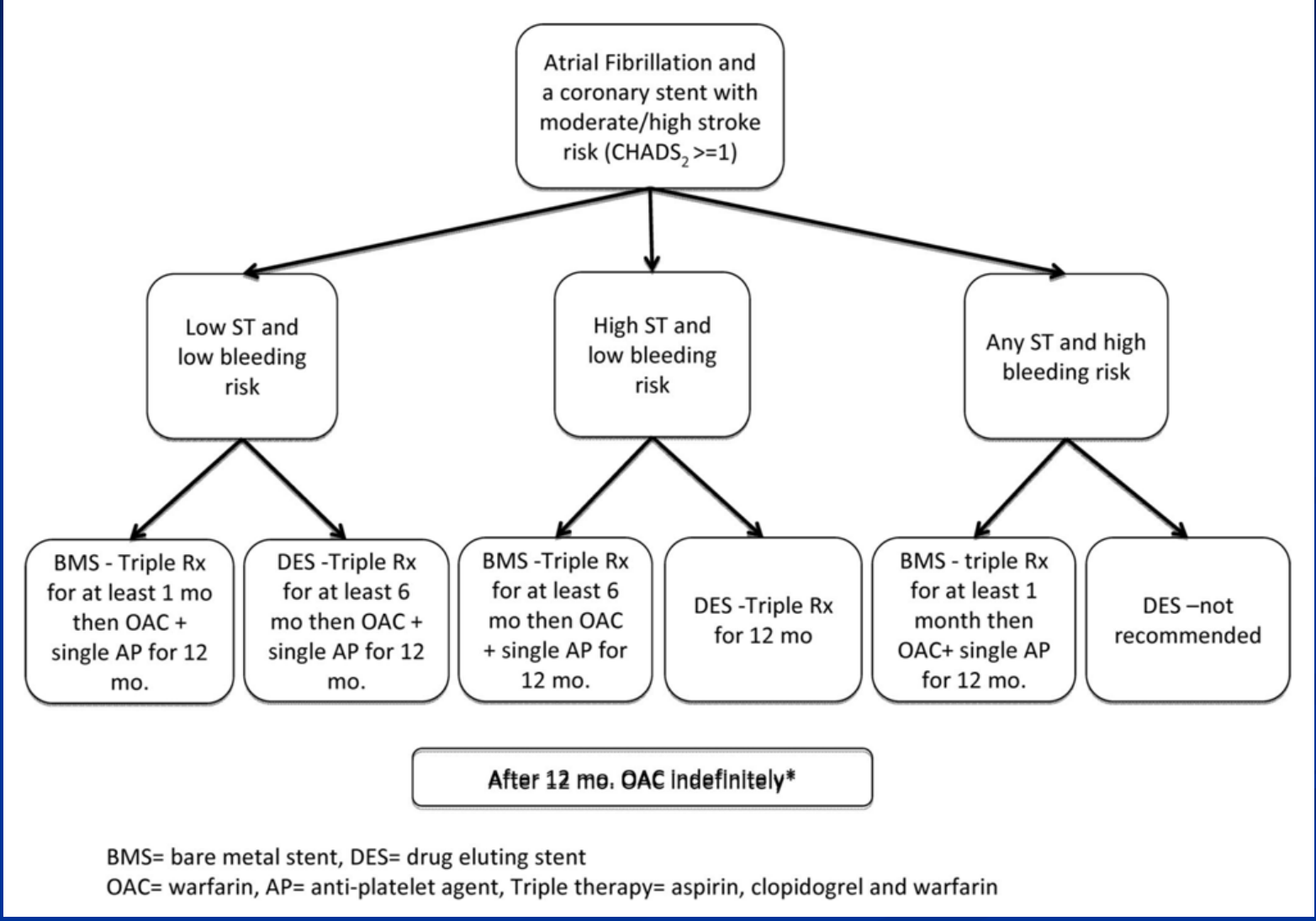
INR, international normalized ratio; ACS, acute coronary syndrome.

[a]Combination of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day may be considered as an alternative.

[b]Drug-eluting stents should be avoided.

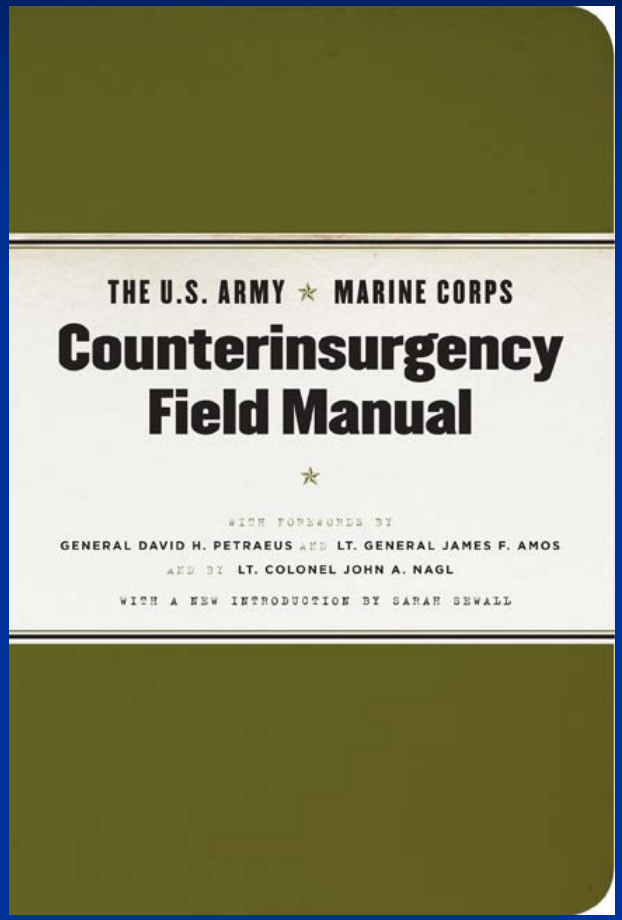
Recommendations for the duration of triple therapy in patients with AF and a coronary stent with moderate/high stroke risk ($CHADS_2$ ≥1).

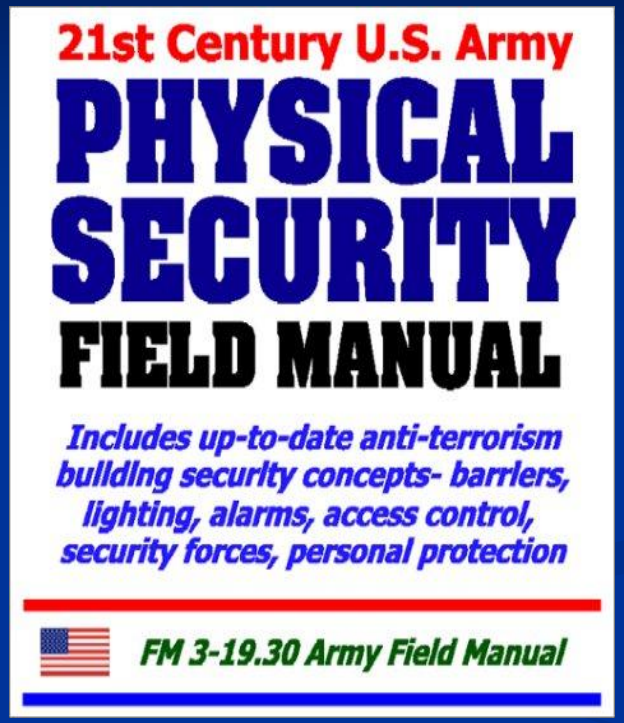
(Faxon et al. Circ Cardiovasc Interv 2011;4:522-34)

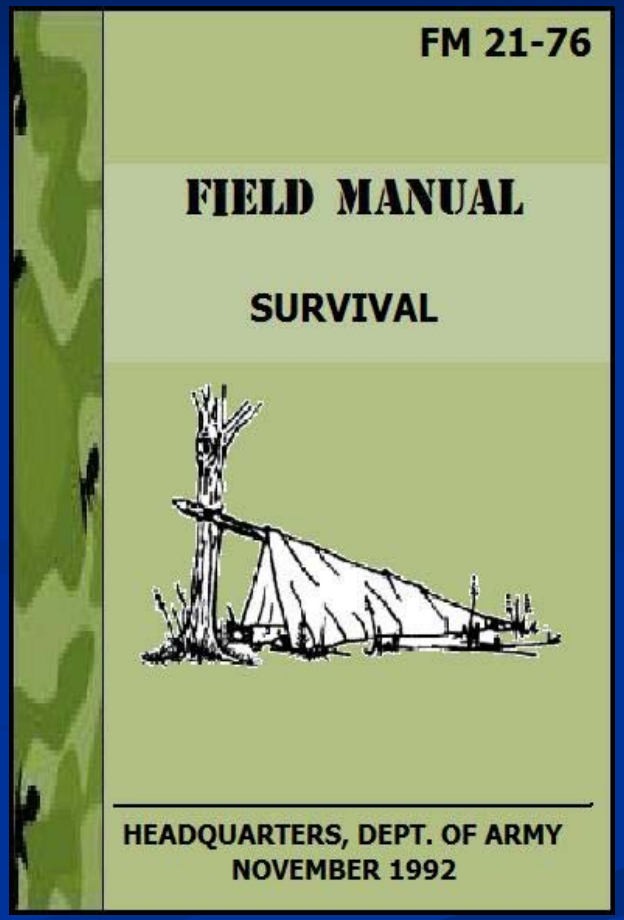


* In patients at high risk for atherothrombotic events including stent thrombosis, continued single antiplatelet therapy with warfarin should be considered after 12 months.

Field Manual





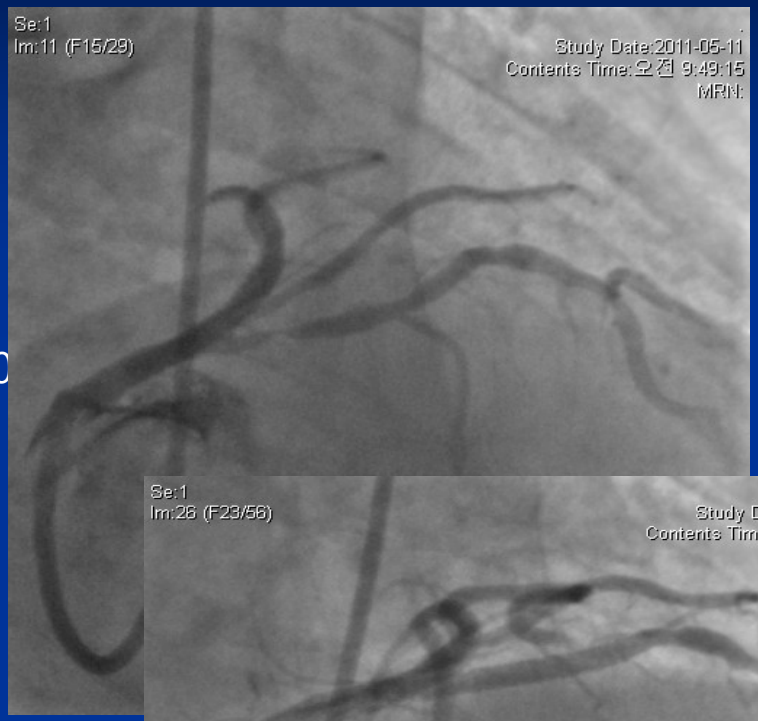


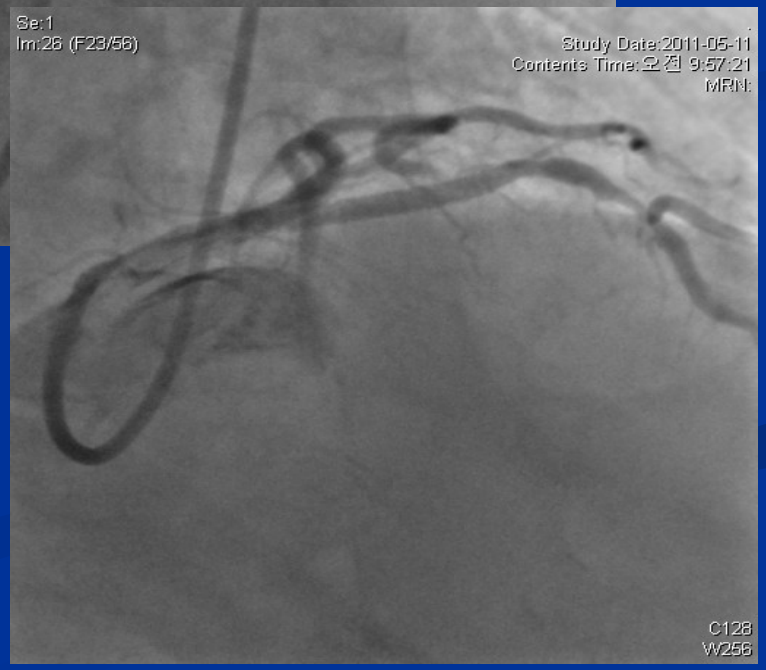
기타 출혈을 줄이는 방법들

- Lower dose aspirin
- Low INR level
- Proton pump inhibitor
- Bare metal stent
- Avoid NSAID
- Access site

Case (2011, 5)

- 74-years old gentleman
- Exertional chest pain
- Warfarin with good INR control
- Ex-smoker, social (?) – drinker
- Past history
  - Small lacunar infarction, left (2009, 10
  - Reflux esophagitis (2008, 04)
  - AF, EF 40-45% (2005, 11)
  - HTN, DM (2000, 03)
- BMS
- Triple therapy
- UGI bleeding + hemoptysis + epistaxis
- Warfarin (2.0 - 2.5)+ ASA 50 mg + PPI





Conclusion

- AF 환자에 PCI-S가 시행되는 경우가 증가하고 있다.
- 많은 변수들에 대한 충분한 고려가 필요할 것으로 생각된다.
  - Warfarin
  - Oculostenotic reflex, knee-jerk reflex
  - BMS
  - POBA / CABG

Physicians more influenced by events induced (**bleeds**) than those prevented (**strokes**)