Azienda Ospedaliero Universitaria Careggi

UNIVERSITÀ DEGLI STUDI FIRENZE

SST Servizio Sanitario della Toscana

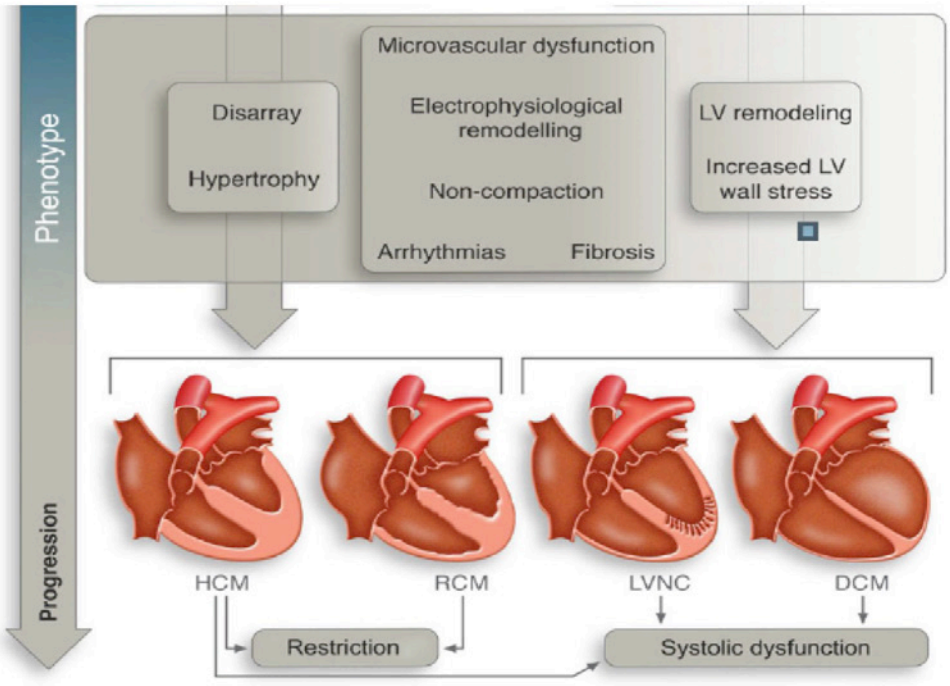
Oltre la fibrillazione atriale non valvolare (FANV): Le altre indicazioni cardiologiche all'anticoagulazione

Malattie primitive del miocardio, trombosi endocavitarie e ipertensione polmonare

Iacopo Olivotto,
Unit Cardiomiopatie
AOU Careggi

Bologna, Savoia Regency Hotel
25-26 gennaio 2018

ANTICOAGULAZIONE
Attualità cliniche e di laboratorio. Aspetti sociali



Olivotto et al Cardiovascular Research 2015

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Cardiomyopathy Unit
Careggi University Hospital - Florence

ESTABLISHED IN 1812 MAY 17, 2012 VOL. 366 NO. 20

Warfarin and Aspirin in Patients with Heart Failure and Sinus Rhythm

Shunichi Homma, M.D., John L.P. Thompson, Ph.D., Patrick M. Pullicino, M.D., Bruce Levin, Ph.D., Ronald S. Freudenberger, M.D., John R. Teerlink, M.D., Susan E. Ammon, N.P., Susan Graham, M.D., Ralph L. Sacco, M.D., Douglas L. Mann, M.D., J.P. Mohr, M.D., Barry M. Massie, M.D., Arthur J. Labovitz, M.D., Stefan D. Anker, M.D., Ph.D., Dirk J. Lok, M.D., Piotr Ponikowski, M.D., Ph.D., Conrado J. Estol, M.D., Ph.D., Gregory Y.H. Lip, M.D., Marco R. Di Tullio, M.D., Alexandra R. Sanford, M.S., Vilma Mejia, B.S., Andre P. Gabriel, M.D., Mirna L. del Valle, B.S., and Richard Buchsbaum, for the WARCEF Investigators*

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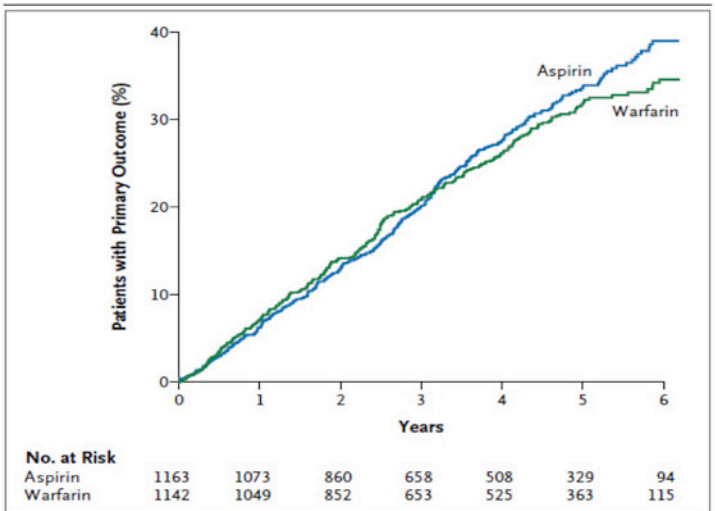

Figure 1. Cumulative Incidence of the Primary Outcome.
The primary outcome was the time to the first event in the composite end point of ischemic stroke, intracerebral hemorrhage, or death from any cause.

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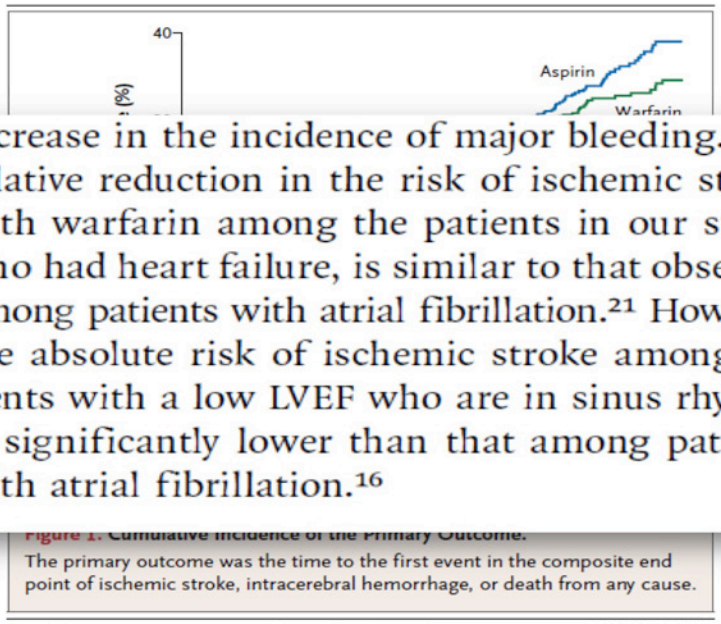

increase in the incidence of major bleeding. The relative reduction in the risk of ischemic stroke with warfarin among the patients in our study, who had heart failure, is similar to that observed among patients with atrial fibrillation.[21] However, the absolute risk of ischemic stroke among patients with a low LVEF who are in sinus rhythm is significantly lower than that among patients with atrial fibrillation.[16]

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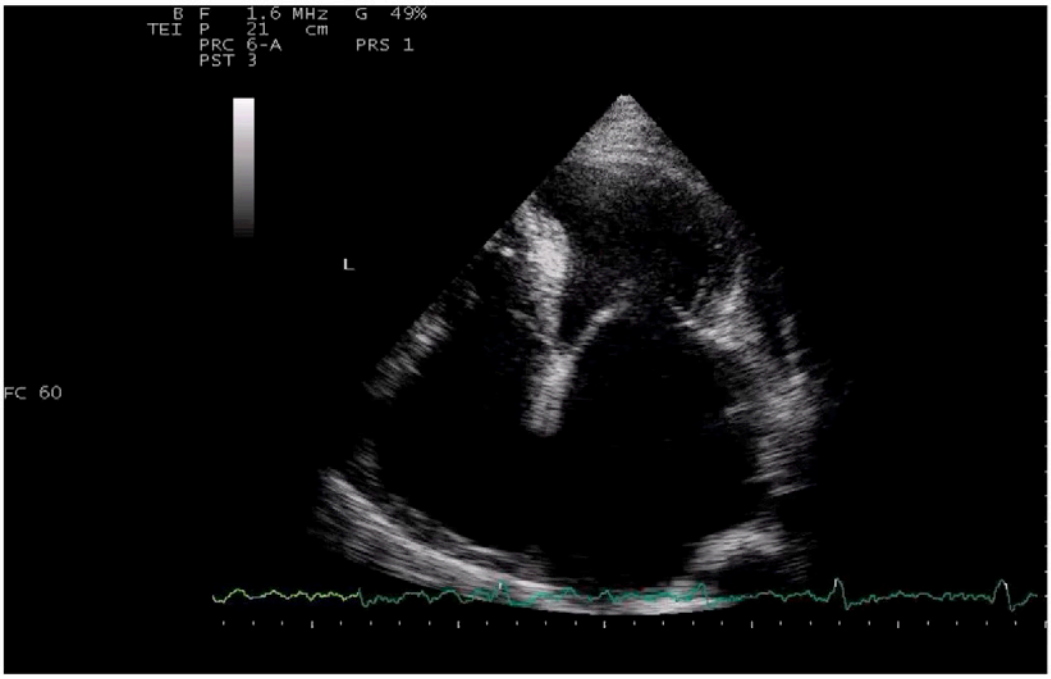
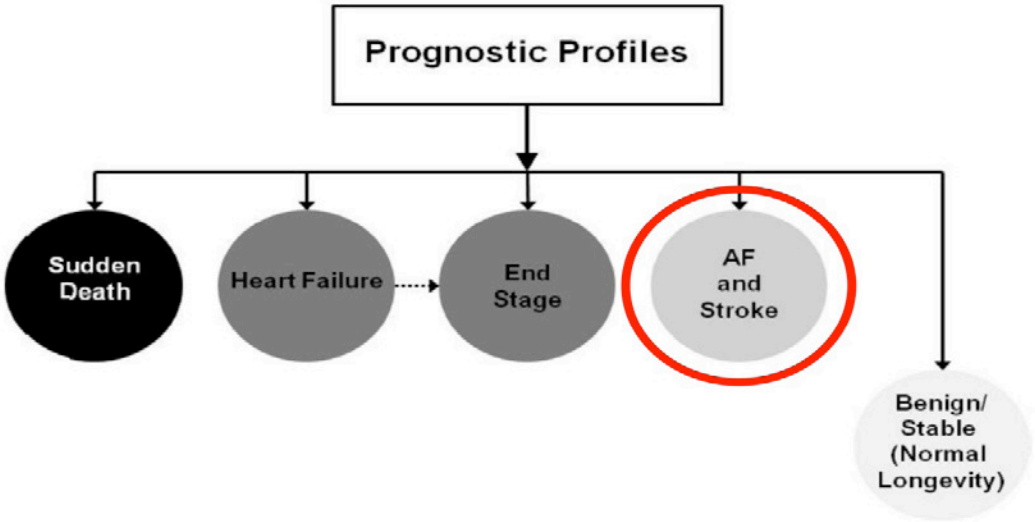
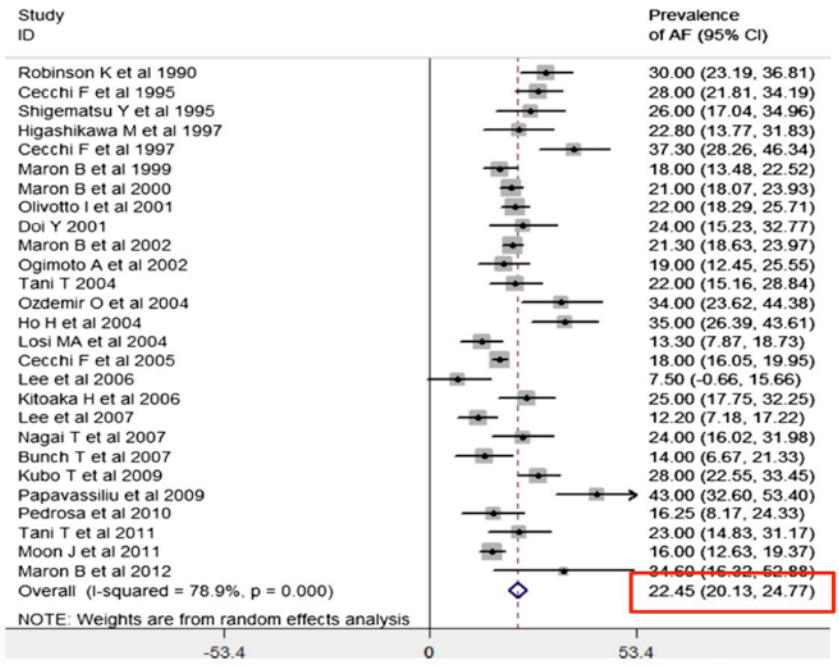




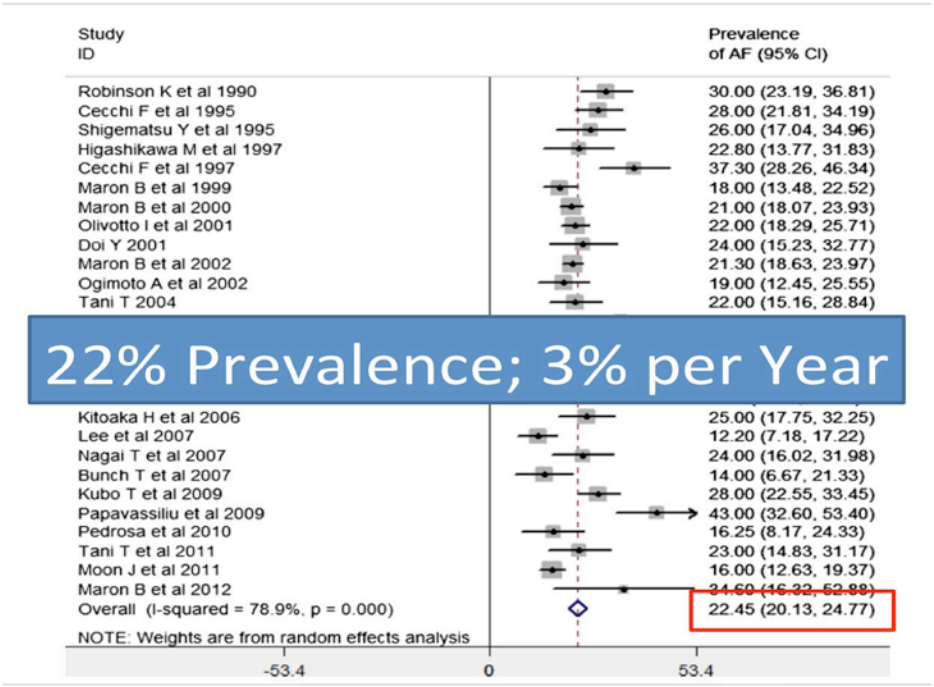
Maron et al, 2003

Prevalence of Atrial Fibrillation in Patients With HCM

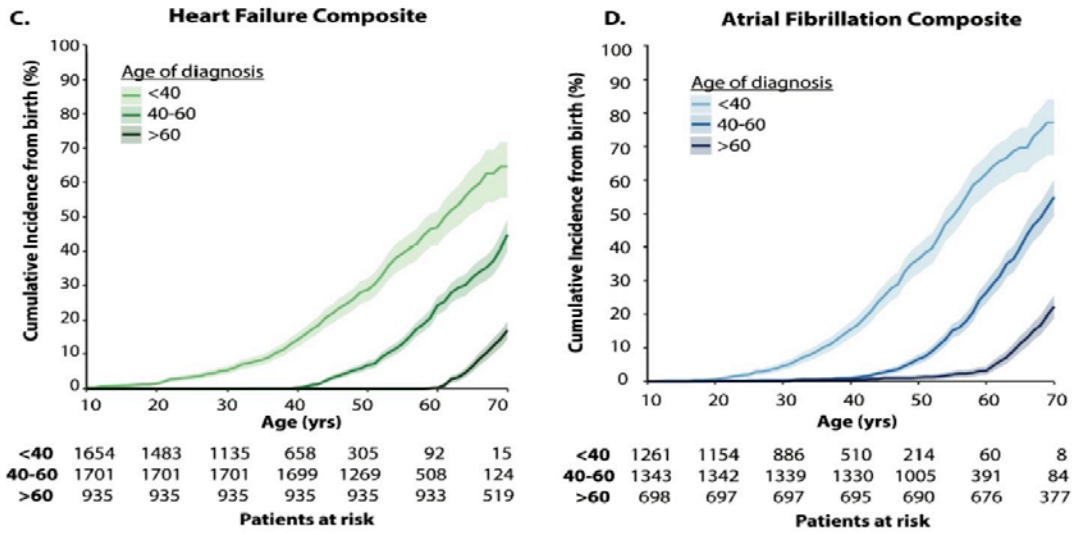


Guttman, Heart 2014

Prevalence of Atrial Fibrillation in Patients With HCM



Guttman, Heart 2014



Ho et al, The ShaRe Registry, Submitted

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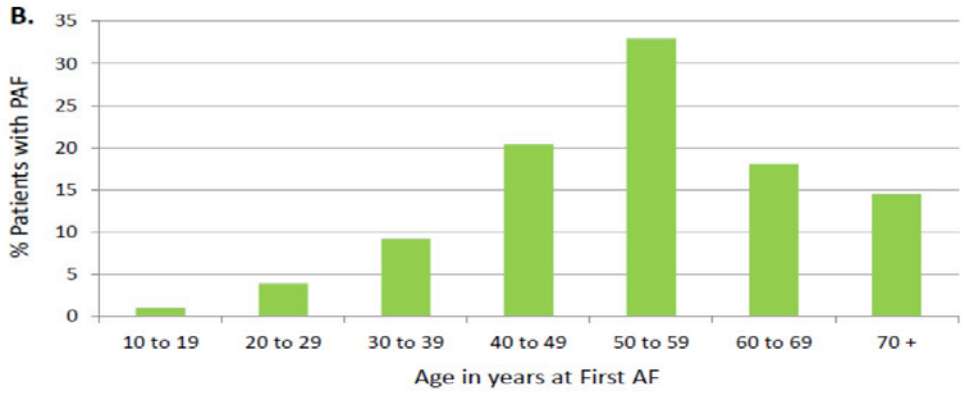
Clinical Profile and Consequences of Atrial Fibrillation in Hypertrophic Cardiomyopathy



Rowin et al, Circulation 2017

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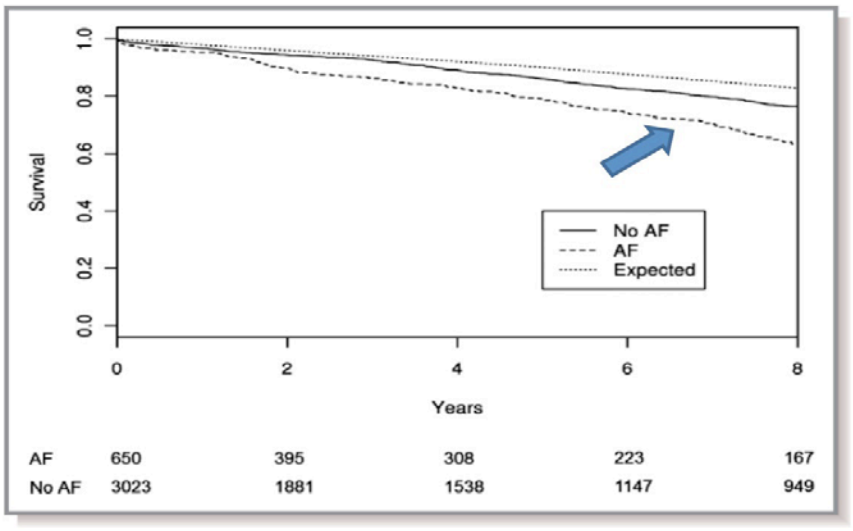
Careggi University Hospital - Florence

Atrial Fibrillation in Hypertrophic Cardiomyopathy: Prevalence, Clinical Correlations, and Mortality in a Large High-Risk Population

Konstantinos C. Siontis, MD; Jeffrey B. Geske, MD; Kevin Ong, MD; Rick A. Nishimura, MD, MACC; Steve R. Ommen, MD, FACC; Bernard J. Gersh, MBChB, DPhil, MACC



N=3673
38% undergoing myectomy or ASA
FU 4.1 (0.2 to 10) years

50% INCREASE IN RISK

J Am Heart Assoc. 2014;3:e001002

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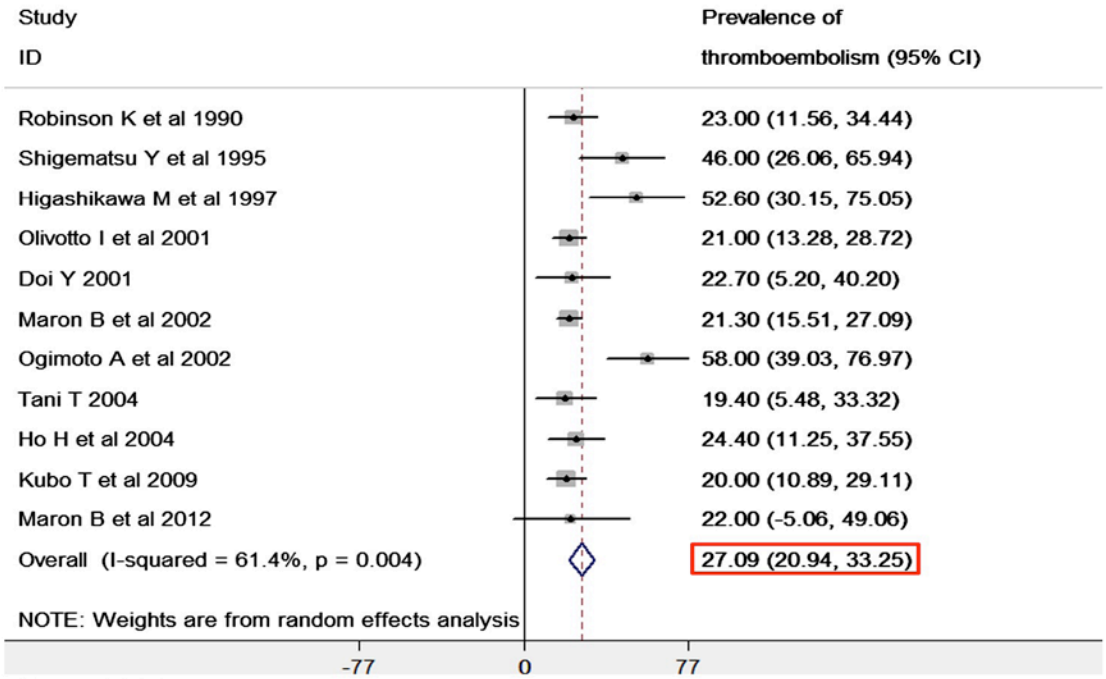
Prevalence of STROKE in HCM Patients with Atrial Fibrillation



Guttman, Heart 2014

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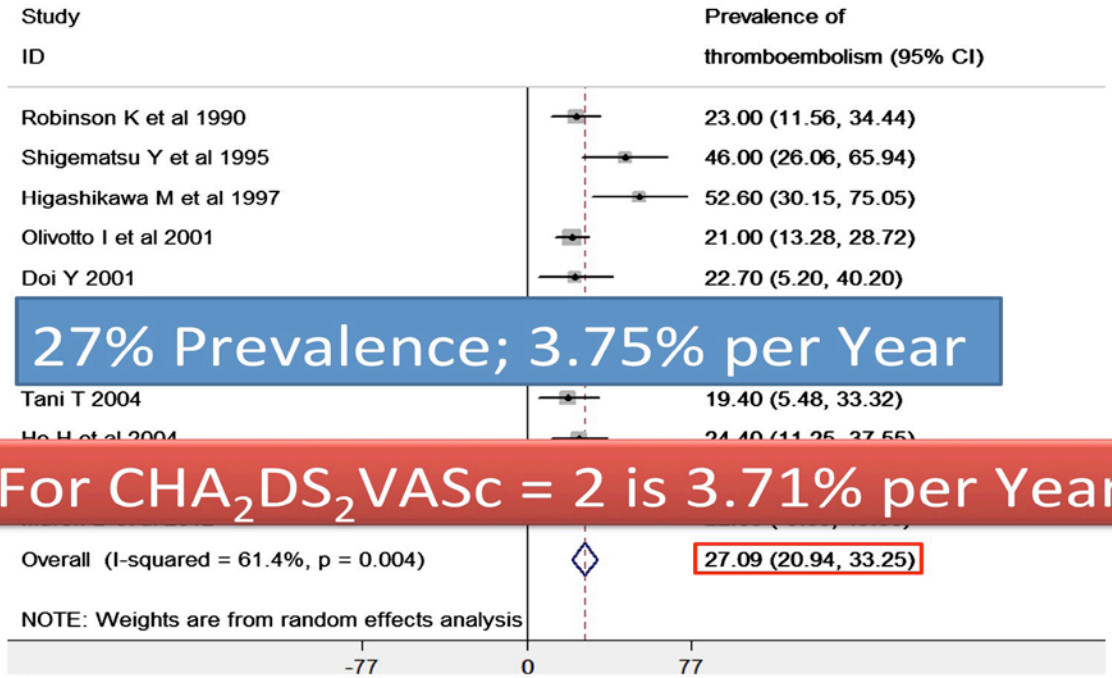
Prevalence of STROKE in HCM Patients with Atrial Fibrillation



Guttman, Heart 2014

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2011 ACCF/AHA Guidelines

Class I

1. **Anticoagulation with vitamin K antagonists (ie, warfarin, to an international normalized ratio of 2.0 to 3.0) is indicated in patients with paroxysmal, persistent, or chronic AF and HCM.[60,430,431] (Anticoagulation with direct thrombin inhibitors [ie, dabigatran§] may represent another option to reduce the risk of thromboembolic events, but data for patients with HCM are not available.[432]) *(Level of Evidence: C)***
2. **Ventricular rate control in patients with HCM with AF is indicated for rapid ventricular rates and can require high doses of beta antagonists and nondihydropyridine calcium channel blockers.[60,430] *(Level of Evidence: C)***

2014 ESC Guidelines

Antiplatelet therapy using aspirin 75–100 mg *plus* clopidogrel 75 mg daily (where there is a low risk of bleeding) should be considered when patients refuse the use of any OAC (whether VKAs or NOACs).	IIa	B	363
When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF—due to failure to maintain therapeutic anticoagulation, side-effects of VKAs, or inability to attend or undertake INR monitoring—a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban) is recommended.	I	B	364,365
Unless there is a reversible cause of AF, lifelong OAC therapy with a VKA (INR 2.0–3.0) is recommended, even if sinus rhythm is restored.	I	C	261,262

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Stroke and Bleeding Risks in NOAC- and Warfarin-Treated Patients With Hypertrophic Cardiomyopathy and Atrial Fibrillation

TABLE 1 Event Rates Per 100 Person-Years and Hazard Ratios in Propensity Score-Matched NOACs Versus Warfarin Users

Outcomes	Event Rate (Per 100 Person-Years) NOACs	Warfarin	Hazard Ratio (95% CI)
Stroke or systemic embolism	1.93	2.03	0.92 (0.32-2.63)
Ischemic stroke	1.61	1.12	1.37 (0.40-4.67)
Hemorrhagic stroke	0.32	0.91	0.35 (0.04-3.36)
Major bleeding	4.18	5.38	0.75 (0.36-1.57)
Intracranial	0.32	1.22	0.26 (0.03-2.25)
Gastrointestinal	3.22	4.06	0.77 (0.33-1.82)

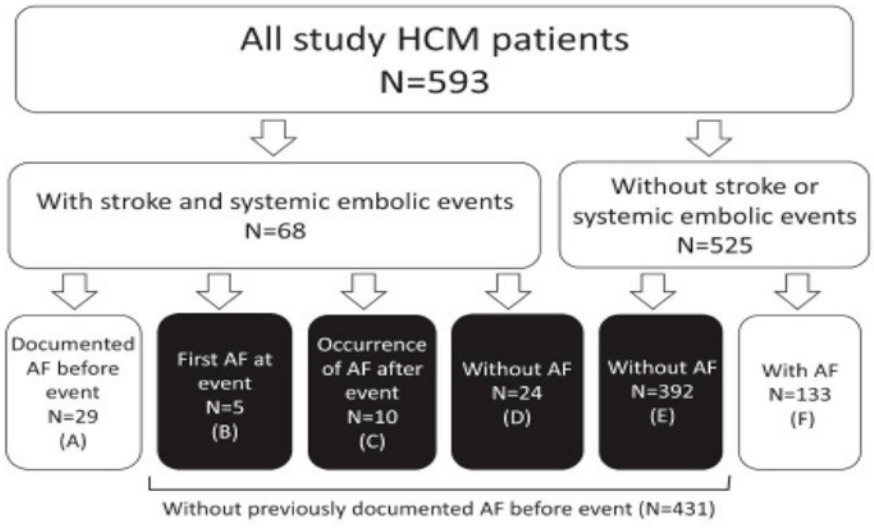
CI = confidence interval; NOAC = non-vitamin K antagonist oral anticoagulants.

Noseworthy, J Am Coll Cardiol 2016

Stroke and Embolic Events in Hypertrophic Cardiomyopathy

Risk Stratification in Patients Without Atrial Fibrillation

Shintaro Haruki, MD, PhD; Yuichiro Minami, MD, PhD; Nobuhisa Hagiwara, MD, PhD



Haruki, Stroke. 2016;47:936-942

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Stroke and Embolic Events in Hypertrophic Cardiomyopathy

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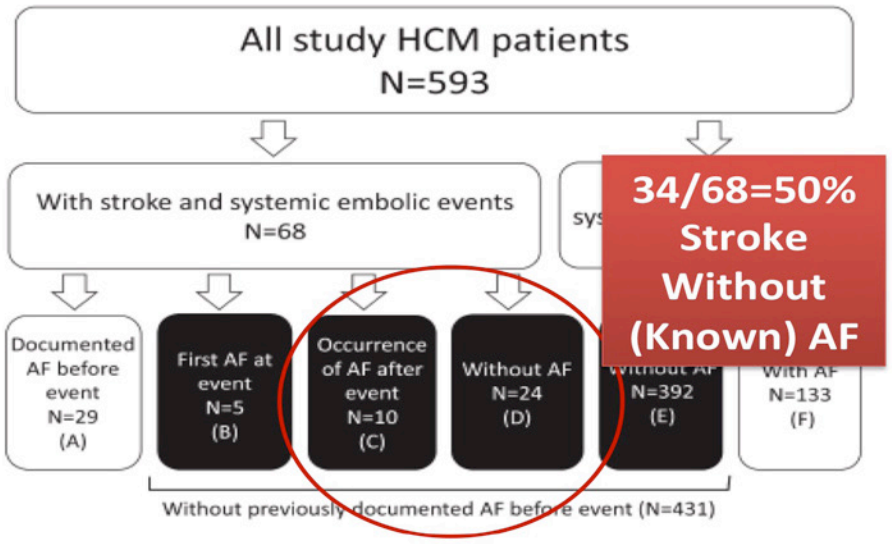

Haruki, Stroke. 2016;47:936-942

HIGH-RISK PATIENTS
(OLDER, LEFT ATRIAL DILATATION, NYHA >1, SV ECTOPIES)

ACTIVE RHYTHM SURVEILLANCE

ADVANCED EVALUATION OF LA FUNCTION

- **Echo – Strain techniques**
- **CMR**

PHARMACOLOGICAL PROPHYLAXIS

- **Antiplatelet Agents**
- **Low dose DOACS**

Arrhythmogenic (RV) Cardiomyopathy

TABLE 3 Predictors of Arrhythmic Risk at Follow-Up

Risk Factor	Univariable Analysis*			Multivariable Analysis*		
	β (SE)	HR (95% CI)	p Value†	β (SE)	HR (95% CI)	p Value
Male	1.01 (0.36)	2.76 (1.37–5.56)	0.005	0.91 (0.36)	2.49 (1.22–5.07)	0.012
Family history of unexplained sudden death	−0.05 (0.30)	0.95 (0.52–1.73)	0.872	–	–	–
Atrial fibrillation	1.26 (0.48)	3.51 (1.38–8.93)	0.008	1.48 (0.48)	4.38 (1.70–11.29)	0.002
History of syncope	1.51 (0.31)	4.54 (2.48–8.34)	<0.001	1.21 (0.34)	3.36 (1.71–6.60)	<0.001
History of HT-MMVT	1.21 (0.30)	3.37 (1.87–6.07)	<0.001	0.79 (0.35)	2.19 (1.12–4.32)	0.023
Participation in strenuous exercise	1.06 (0.48)	2.90 (1.14–7.38)	0.026	1.09 (0.50)	2.98 (1.12–7.90)	0.028
Age at presentation ≤20 yrs vs. >40 yrs	−0.36 (0.57)	0.70 (0.23–2.14)	0.530	–	–	–
Age at presentation 21–40 yrs vs. >40 yrs	1.07 (0.33)	2.91 (1.51–5.58)	0.001	–	–	–
Proband status‡	1.26 (0.39)	3.54 (1.65–7.59)	0.001	–	–	–
Negative T waves in leads V_1–V_3	0.48 (0.31)	1.62 (0.88–2.99)	0.121	–	–	–
Nonsustained VT	0.34 (0.30)	1.40 (0.78–2.51)	0.256	–	–	–
PVC count >1,000/day	0.01 (0.39)	1.01 (0.47–2.18)	0.984	–	–	–

*Estimates from univariable and multivariable Cox regression models predicting life-threatening arrhythmic events after presentation in 267 patients who did not present with an LAE. †p values differ slightly from those presented in Figure 3 and in Online Figures 3 and 4 due to the use of the Wald test based on Cox regression models as opposed to the log-rank test statistic. ‡The significance of "proband status" at univariable analysis was not retained in the multivariable model, due to its strong correlation with the history of syncope and the history of HT-MMVT (25 of 27 patients with syncope and 37 of 39 patients with HT-MMVT were also probands).

CI = confidence interval; HR = hazard ratio; HT-MMVT = hemodynamically tolerated sustained monomorphic ventricular tachycardia; PVC = premature ventricular contraction; SE = standard error; other abbreviations as in Table 1.

Mazzanti et al, J Am Coll Cardiol 2016

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Arrhythmogenic (RV) Cardiomyopathy

TABLE 3 Predictors of Arrhythmic Risk at Follow-Up

AF occurred at presentation in only 3% of the patients. However, over half of the patients with AF at presentation had a structurally normal heart when the arrhythmia occurred.

*Estimates from univariable and multivariable Cox regression models predicting life-threatening arrhythmic events after presentation in 267 patients who did not present with an LAE. †p values differ slightly from those presented in Figure 3 and in Online Figures 3 and 4 due to the use of the Wald test based on Cox regression models as opposed to the log-rank test statistic. ‡The significance of "proband status" at univariable analysis was not retained in the multivariable model, due to its strong correlation with the history of syncope and the history of HT-MMVT (25 of 27 patients with syncope and 37 of 39 patients with HT-MMVT were also probands).

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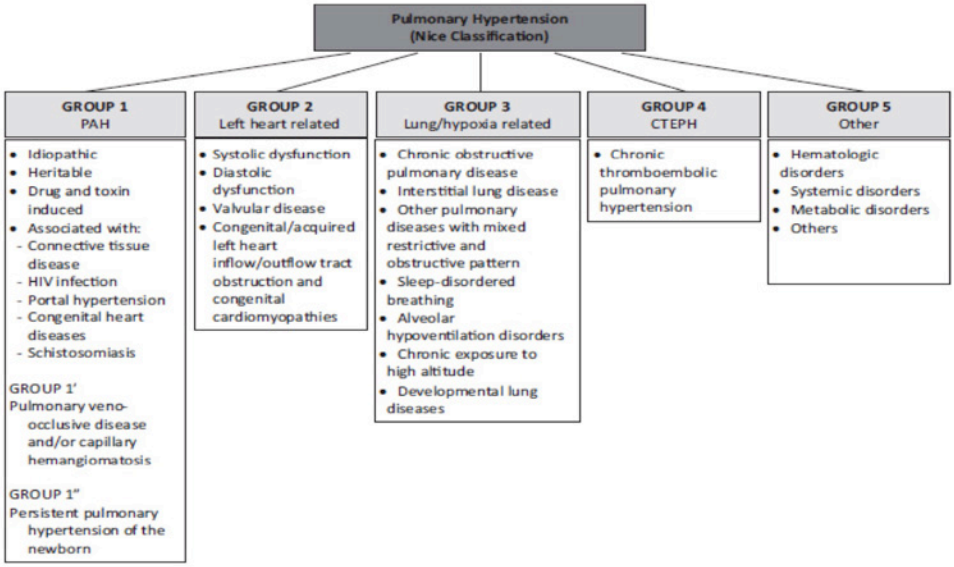
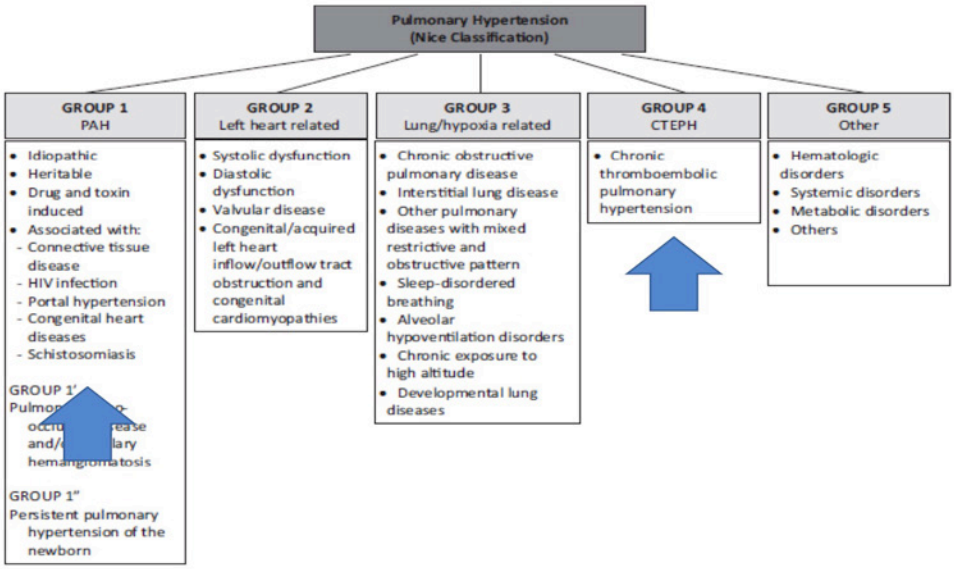


Figure 1 Updated classification of pulmonary hypertension from the 5th World Symposium on Pulmonary Hypertension, Nice (2013). CTEPH, chronic thromboembolic pulmonary hypertension; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension.

152 The Journal of Heart and Lung Transplantation, Vol 35, No 2, February 2016



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Anticoagulation in PAH: Rationale

- Post-mortem evaluation demonstrated vascular thrombotic lesions
- Endothelial cell dysfunction

Δ Thrombomodulin/PC	Δ PAI-1
ΔtPA	Δ vWF
ΔPLT	Δ Proliferation Mediators

- Conditions associated with PAH

AF	VTE
APS and CTD	Chronic PE
Valvular Disease	Central Venous Catheters

Anticoagulation in PAH

Roldan et al. 2017

The Journal of Heart and Lung Transplantation

Table 1 Recommendation of Anticoagulation in Pulmonary Arterial Hypertension

PAH etiology	American Guidelines (2009)[7] and updated algorithm from Fifth WSPH, Nice (2013)[8] Class of recommendations[a]/ level of evidence[b]	Targeted INR	European Guidelines (2015)[6] Class of recommendations[a]/ level of evidence[b]	Targeted INR
IPAH	IIa/C	1.5–2.5	IIb/C	2.0–3.0
Heritable	IIa/C		IIb/C	
Due to anorexigens	IIa/C		IIb/C	
APAH				
Connective tissue disease	IIb/C		Anticoagulation may be considered an individual basis in the presence of thrombophilic predisposition	IIb/C
HIV infection			Anticoagulation is not recommended because of lack of data	III/C
Portal hypertension			Anticoagulation is not recommended	III/C
Congenital cardiac shunts			With no significant hemoptysis, anticoagulation may be considered in patients with PA thrombosis or signs of heart failure	IIb/C

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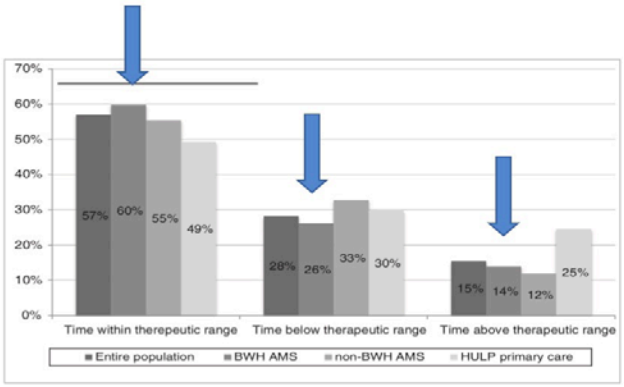
Assessment of the quality of anticoagulation management in patients with pulmonary arterial hypertension

Roldan et al. 2017



TTR (>60%)=57%

- Higher in OAC Dedicated Centers

Events (100pts/years)	TTR<60	TTR>60	p
Thrombosis	1.5	0.6	ns
Major Bleeding	5.9	6.0	ns
Survival Analysis			
5-year thrombosis-free survival	89.2%	96.8%	ns
5-year bleeding-free survival	66.9%	76.1%	ns

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Efficacy of OAC and survival

Even though many **retrospective** studies show a survival benefit of OAC treatments, results have to be **weighed againts** methodological limitations such as:

- retrospective design,
- high dropout rates,
- Variability across centers in data presentation, events/outcomes.

This holds true specifically for two subgroups of PAH:

Idiopathic PAH (IPAH)

CTD-PAH (i.e. SScPAH etc.)

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COMPERA vs REVEA

Circulation

ORIGINAL ARTICLE

Anticoagulation and Survival in Pulmonary Arterial Hypertension

Results From the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA)

ORIGINAL ARTICLE

Effect of Warfarin Treatment on Survival of Patients With Pulmonary Arterial Hypertension (PAH) in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL)

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COMPERA vs REVEA

Circulation

COMPERA	REVEAL
Anticoagulation is associated with an **improved three-year survival** in patients with **IPAH** compared with those who had other forms of PAH. • HR= **0.79**; 95% CI 0.66-0.94	**No survival advantage** associated with warfarin use in patients **with IPAH** compared with **matched** warfarin-naïve **PAH controls**, even when adjusted for disease severity.
SSc-PAH there was a statistically **nonsignificant trend towards worse survival** among those taking anticoagulants compared with patients not on anticoagulant therapy. • HR=**1.82**; 95% CI 0.94-3.54	**SSc-PAH:** ↑+50% mortality patients receiving warfarin, when compared with PAH patients who were not anticoagulated.

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NOACS: SPHInX Trial and TRAPS

BMJ Open Multicentre randomised placebo-controlled trial of oral anticoagulation with apixaban in systemic sclerosis-related pulmonary arterial hypertension: the SPHInX study protocol

Study design:

- **Multicentre RCT** will compare **2.5 mg apixaban with placebo,** in parallel treatment groups randomised in a 1:1 ratio, IN SSc-PAH
- **twice daily** for **3 years** as adjunct therapy to stable oral PAH therapy.

Outcome measures:

- Primary composite: time to death or clinical worsening of PAH.
- Secondary outcomes: functional capacity, health-related quality of life measures and adverse events. A cost-effectiveness analysis

ClinicalTrials.gov

Rivaroxaban in Thrombotic Antiphospholipid Syndrome (TRAPS)

Study Design:

- **multicentre**, interventional, prospective, parallel, **randomised, controlled**, open-label, **Rivaroxaban 20 mg qd** vs warfarin (INR target 2.5), in triple aPL-positive APS patients.

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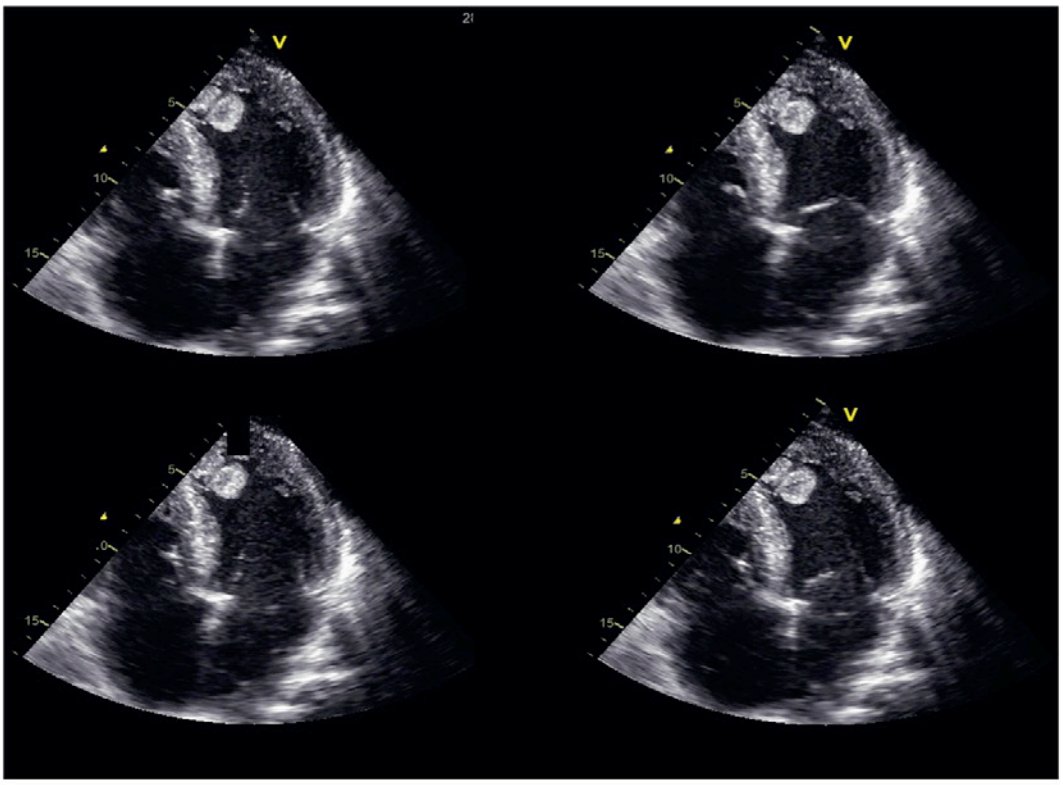

Delewi, Heart 2012;98:1743–1749

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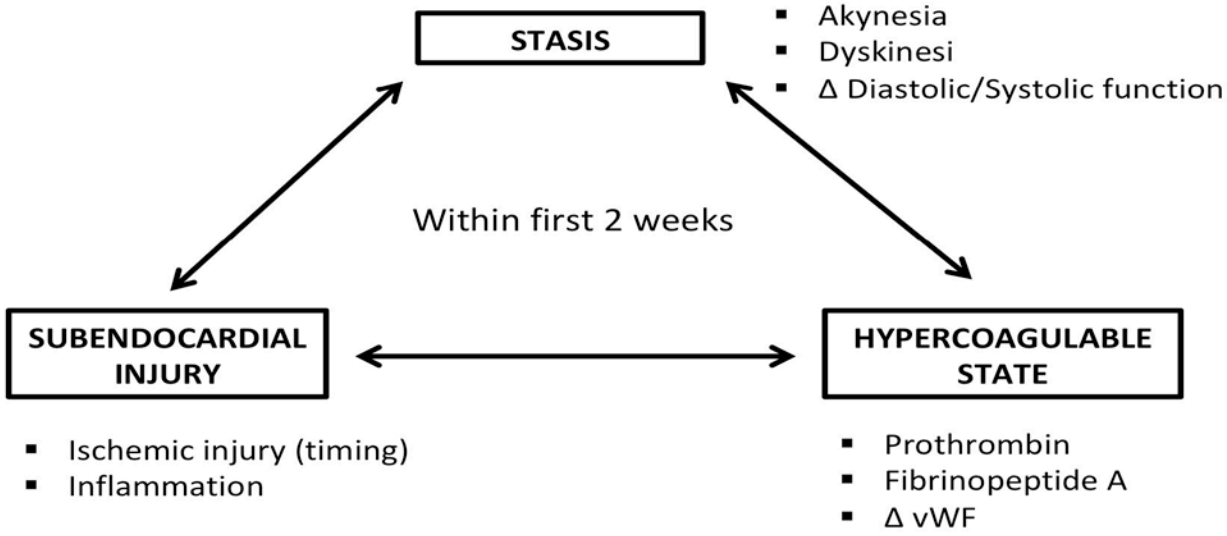
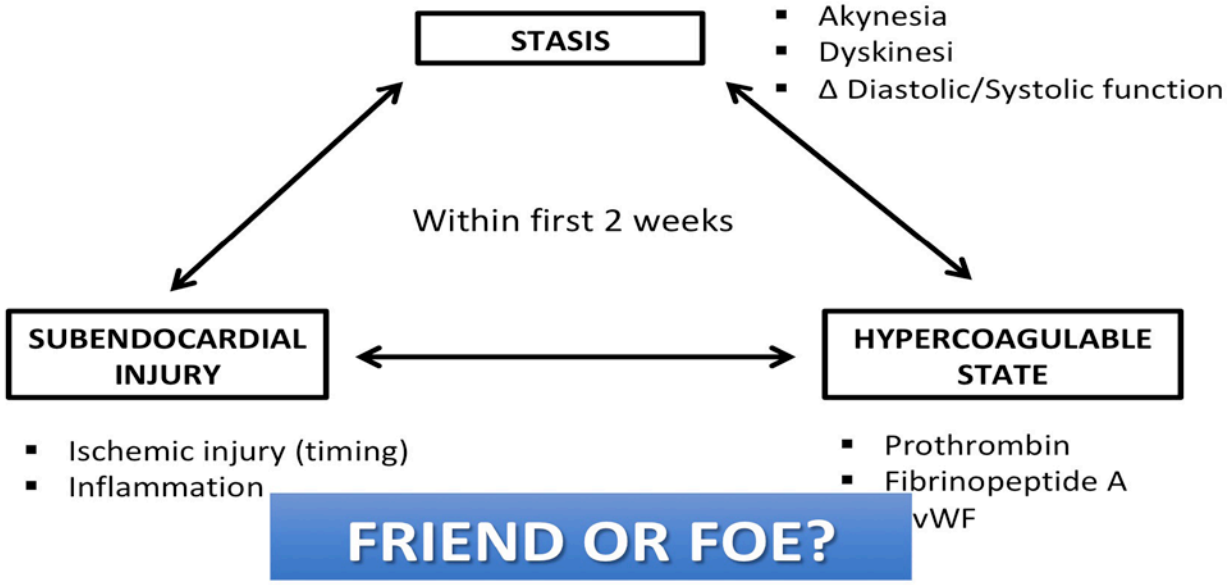
Pathogenesis of LV Thrombosis



Pathogenesis of LV Thrombosis



Incidence of LVT in AMI

Pre-PCI era

- Incidence: up to 46% of first anterior wall STEMI
- Systemic Embolism: >20%
- Overall poor prognosis
- Proper Anticoagulation: ~ 6 months

Introduction of Primary PCI

- Incidence decreased to 5-15%
- Benefits of DAPT
- Which patients benefit from of prophylactic DAPT+ anticoagulation
  - Potential new role of NOACs

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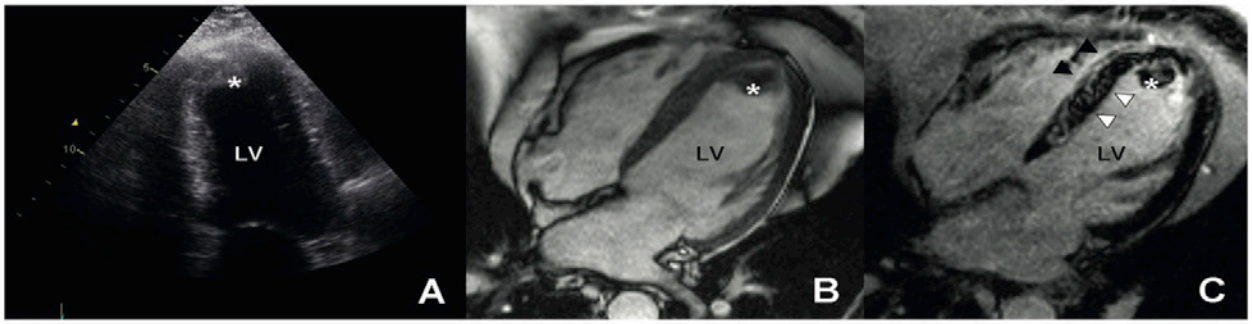
LVT Detection

Delewi et al. Heart 2012 Heart

	Sensitivity	Specificity
TOE	35%	90%
Routine clinical TTE	35—40%	90%
TTE (indication suspect LV thrombus)	60%	90%
CT	Comparable with TTE	
Cine CMR	60%	90%
DE-CMR	88%	99%

CMR, cardiac magnetic resonance imaging; **CT**, computed tomography; **DE**, delayed enhancement; **LV**, left ventricular; **TOE**, transoesophageal echocardiography; **TTE**, transthoracic echocardiography.



LVT Treatment

- Thrombolysis
- Heparin
- VKAs in Triple Therapy (3-6 months)
- DOAC: no data (yet)

LMWH vs VKAs (LMWH less expensive but trend towards more thrombosis)

White et al, AMJ 2015

Anticoagulation combined with antiplatelet therapy in patients with left ventricular thrombus after first acute myocardial infarction

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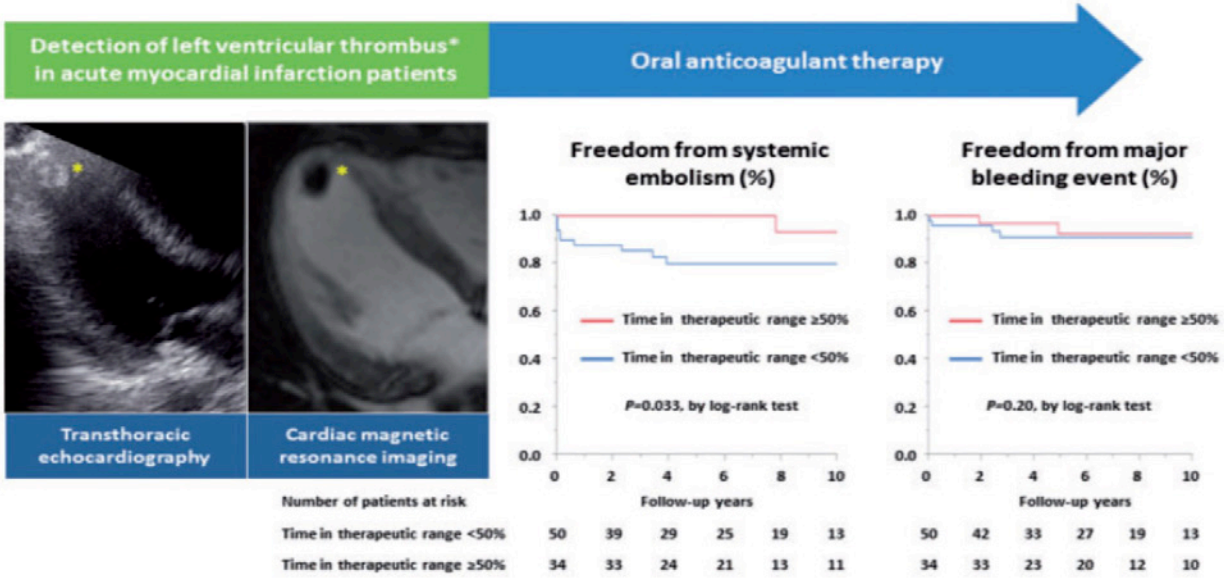
European Heart Journal (2018) 39, 201–208



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NOACS vs VKA in CAD

Rivaroxaban

- PIONEER-AF PCI
- RT-AF
- GEMINI-PCI

Apixaban

- AUGUSTUS (Apixaban) (patients with AF and recent coronary event).
- NCT02982590 (Apixaban vs VKAs in Patients With Left Ventricular Thrombus)

CONCLUSIONS

- "Other" indications for anticoagulation remain a moving target and often a data-free zone
- Changing clinical scenario (AMI but also PAH and myocardial diseases)
- Increasingly effective background therapy
- Common clinical sense in the assessment of individual patients is still as important as guidelines

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TOXICOLOGY OBSERVATION

Positive Outcome After Intentional Overdose of Dabigatran

Jason S. Woo · Neel Kapadia · Sarah E. Phanco · Catherine A. Lynch

Abstract
Introduction Dabigatran (Pradaxa™), an orally active direct thrombin inhibitor, was approved by the United States Food and Drug Administration for the prevention of stroke in patients with atrial fibrillation in October 2010. Life-threatening consequences from dabigatran therapy include hemorrhage and bleeding complications, but they typically occur after renal impairment. We describe the first case report of intentional, acute overdose with dabigatran.
Case Report A 57-year-old woman with a medical history of depression and atrial fibrillation presented to the emergency department after ingesting 11.25 g of dabigatran in a suicide attempt. Despite an ecchymosis indicative of prior trauma, there was no evidence of acute bleeding. After receiving gastric lavage and activated charcoal therapy in the emergency department, she was admitted to the ICU. On presentation, dabigatran blood levels measured 970 ng/mL and thrombin clot times measured above the testable limits (>120 s) until 52 h post-arrival. The remainder of her clinical course was uncomplicated, and the patient was transferred to an inpatient psychiatric unit for depression follow-up.
Discussion This case shows the clinical course of a patient with an acute, massive dabigatran overdose with no significant clinical consequences. Currently, there is no ideal method to monitor anticoagulation levels; there is no pharmacologic reversal method, and hemodialysis is an undesirable treatment option.

Keywords Pradaxa · Toxicity · Anticoagulation · Bleed · Hemorrhage

Introduction