Update in EP 2010

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UPDATE in EP

- ✓Atrial Fibrillation
- ✓Ventricular Arrhythmias
- ✓Implantable Devices

Atrial Fibrillation

- ✓ Dabigatran versus Warfarin in Patients with AFib
  RE-LY (Randomized Evaluation of Long- Term Anticoagulation Therapy) study (N Engl J Med 2009;361:1139-51)
- ✓ PROTECT AF (WATCHMAN-Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) (*Lancet* 2009; 374: 534–42)
- ✓ Effect of Clopidogrel Added to Aspirin in Patients with AF (The ACTIVE Study (N Engl J Med 2009;360:2066-78)
- ✓ Analysis of Stroke in ATHENA (*Circulation*. 2009;120:1174-1180)
- ✓ Comparison of AAD Therapy and RF Catheter Ablation in Patients With PAF (ThermoCool AF trial) (*JAMA. 2010;303(4):333-340*)
- ✓ Long-term Outcomes in Individuals With Prolonged PR Interval or First-Degree AVB (*JAMA. 2009;301(24):2571-2577)*

Atrial Fibrillation

- ✓ AF is the most common sustained cardiac arrhythmia
- ✓ Since AF mainly affects elderly people, its prevalence is expected to increase in parallel with the increasing age of the population
- ✓ The lifetime risk for development of AF is one in four in men and women 40 years of age and older
- ✓ Stroke, the most serious complication of AF, occurs in 5% of non-anticoagulated patients every year
- ✓ The risk of stroke increases substantially with age, from 1.5% in individuals aged 50–59 years to 23.5% for those aged 80–89 years
- ✓ Stroke is the third most frequent cause of death in the USA and the leading cause of serious disability
- ✓ Therefore, stroke prophylaxis is a crucial component of management of AF

Atrial Fibrillation (AF)

- ✓ Warfarin remains the most efficacious therapy to prevent stroke in AF

- ✓ **Limitations of the warfarin:**
  - -increased risk of hemorrhagic stroke
  - -food and drug interactions
  - -need for ongoing monitoring

- ✓ This year, several studies examining new therapies for stroke prevention in AF were published.

Dabigatran versus Warfarin in Patients with AFib

RE-LY (Randomized Evaluation of Long- Term Anticoagulation Therapy) study (N Engl J Med 2009;361:1139-51)

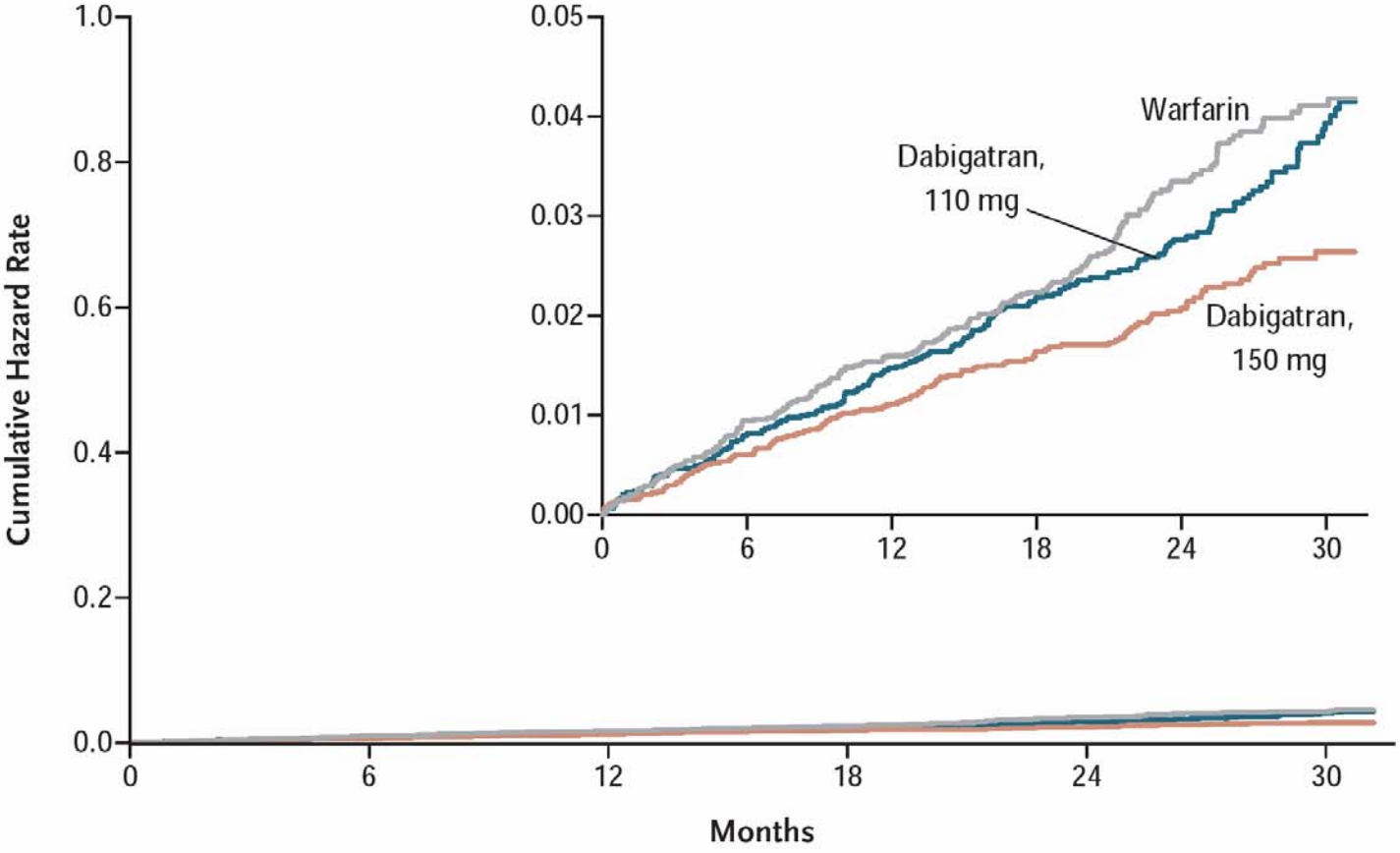
- ✓ a randomized blinded trial in patients with AF and $CHADS_2$>0
- ✓ direct thrombin inhibitor
  - -110mg dabigatran
  - -150mg dabigatran
- ✓ Warfarin
- ✓ A total of 18,113 AF patients were enrolled, with median follow-up of 2.0 years

Results

- ✓ **The primary outcome of stroke or systemic embolism occurred:**
  - -In 182 patients receiving 110 mg twice daily of dabigatran (1.53% per year)
  - -In 134 patients receiving 150 mg twice daily of dabigatran (1.11% per year)
  - -and in 199 patients receiving warfarin (1.69% per year)

- ✓ Both doses of dabigatran were noninferior to warfarin ($p<0.001$)

- ✓ The higher dose of dabigatran was also superior to warfarin (relative risk=0.66, 0.53 to 0.82, $p<0.001$)



No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

Rates of hemorrhagic stroke and Major bleeding

- ✓ Rates of hemorrhagic stroke were significantly smaller for either dose of dabigatran compared to warfarin

  -RR for

  Dabigatran 110mg, RR=0.31, $p<0.001$

  Dabigatran 150mg, RR=0.26, $p<0.001$

compared to warfarin

- ✓ Major bleeding was:

  -similar between the 150-mg dose of dabigatran and warfarin

  -but significantly less in the 110-mg dose of dabigatran compared with warfarin (RR=0.80, p=0.003)

- ✓ Major GI bleeding was significantly higher with dabigatran 150mg compared with warfarin

Conclusions

- ✓ The RE-LY study suggests that dabigatran may be an acceptable alternative to warfarin in AF patients with additional risk factors for stroke

- ✓ The higher dose:
  - May have more efficacy
  - Comparablerisk of hemorrhagic stroke and major bleeding to that of warfarin
  - and higher risk of GI bleeding than that of warfarin

- ✓ The lower dose:
  - Have comparable efficacy to warfarin
  - With evidence that there may be a lower bleeding risk

- ✓ Therefore, future research, clinical experience, and expert consensus may teach us how to best risk stratify to determine optimal dosing for individual patients

Conclusions

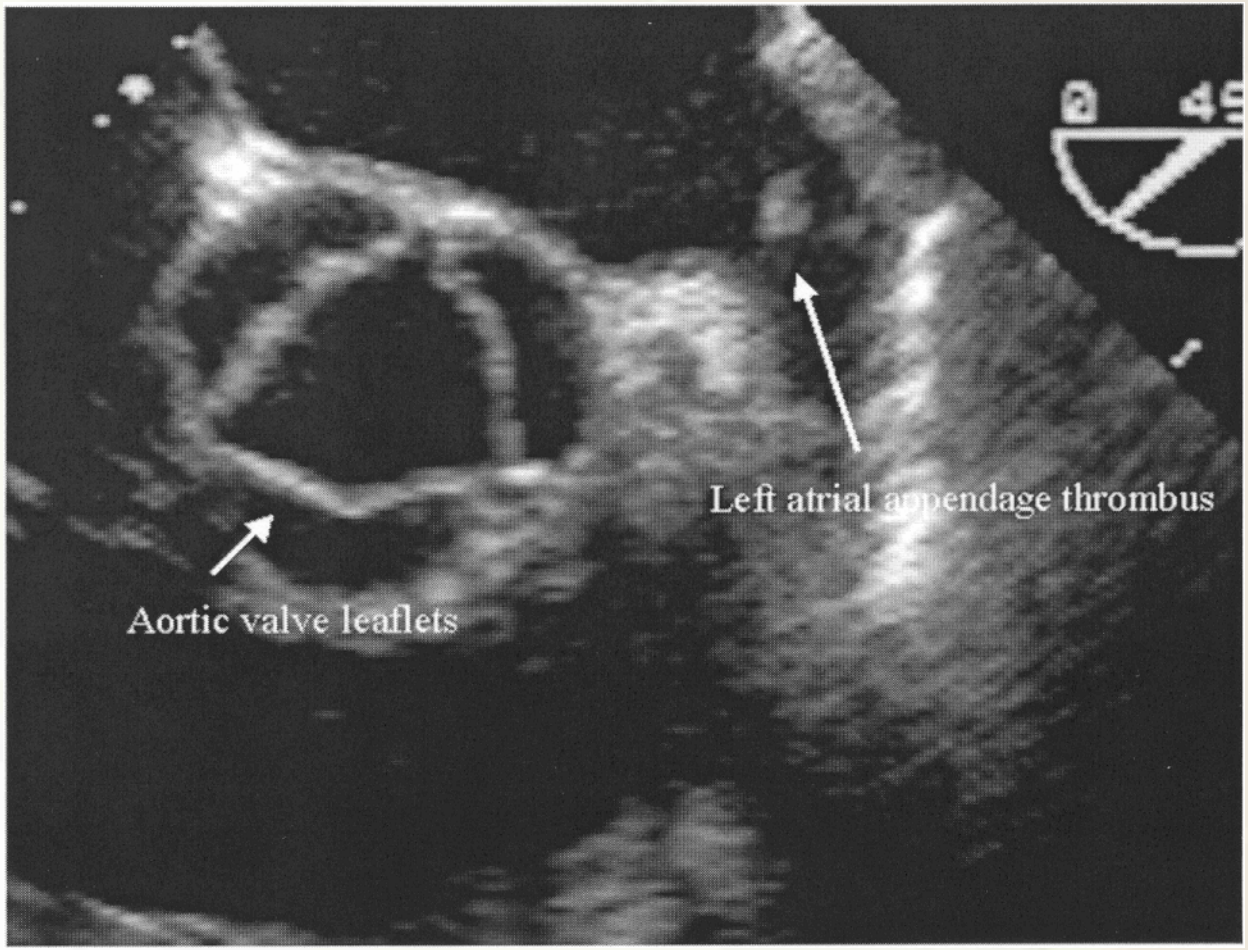
- ✓ About 80% of the active drug is:
  - excreted by the kidneys
  - and a creatinine clearance <30 ml was an exclusion criterion for the trial
- ✓ Therefore, patients with significant renal impairment may not be candidates for this new therapy
- ✓ In addition, to enhance absorption of dabigatran, a low pH is required
  - Therefore, the dabigatran capsules contain dabigatran-coated pellets with a tartaric acid core
  - This may explain the dyspepsia and higher rates of gGI bleeding with the higher dose
- ✓ It also suggests that H2-blockers and proton pump inhibitors might affect the absorption and potentially reduce the efficacy of the drug

PROTECT AF (WATCHMAN-Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation)

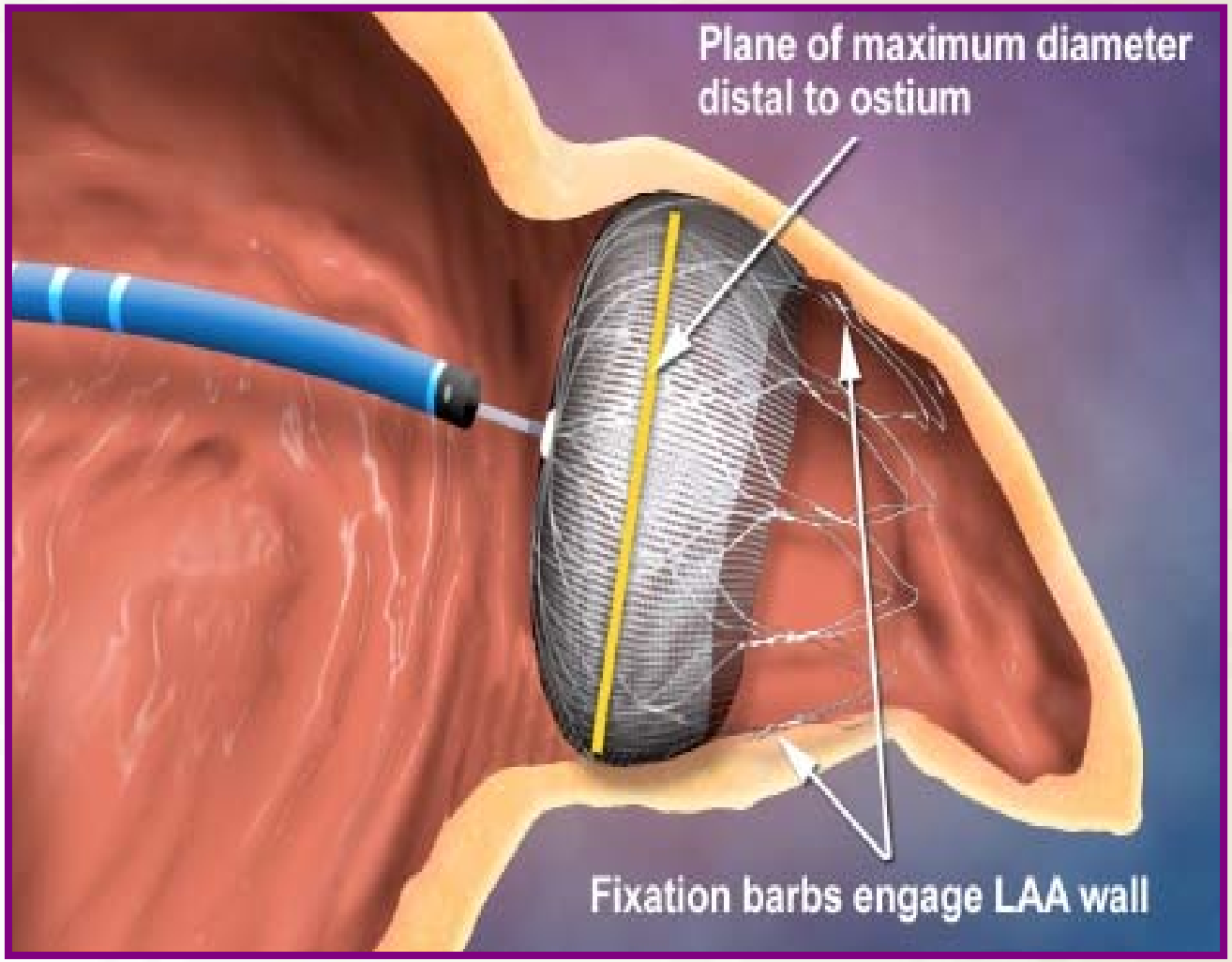
(*Lancet* 2009; 374: 534–42)

- ✓ Based on the findings that the left atrial appendage is the source of thrombi in more than 90% of patients with AF
- ✓ This trial investigate the WATCHMAN device
  - a self expanding nickel titanium (nitinol) frame structure with fixation barbs and a permeable polyester fabric cover implanted via a transseptal approach to seal the left atrial
- ✓ PROTECT AF enrolled 707 AF patients with an additional risk factor for stroke randomly assigned in a 2:1 ratio to percutaneous closure of the left atrial appendage or warfarin therapy
- ✓ The device was successfully implanted in 88% of those assigned to the intervention

Thrombi Formation in the LAA



WATCHMAN – LAA Closure Device



Key Participation Criteria

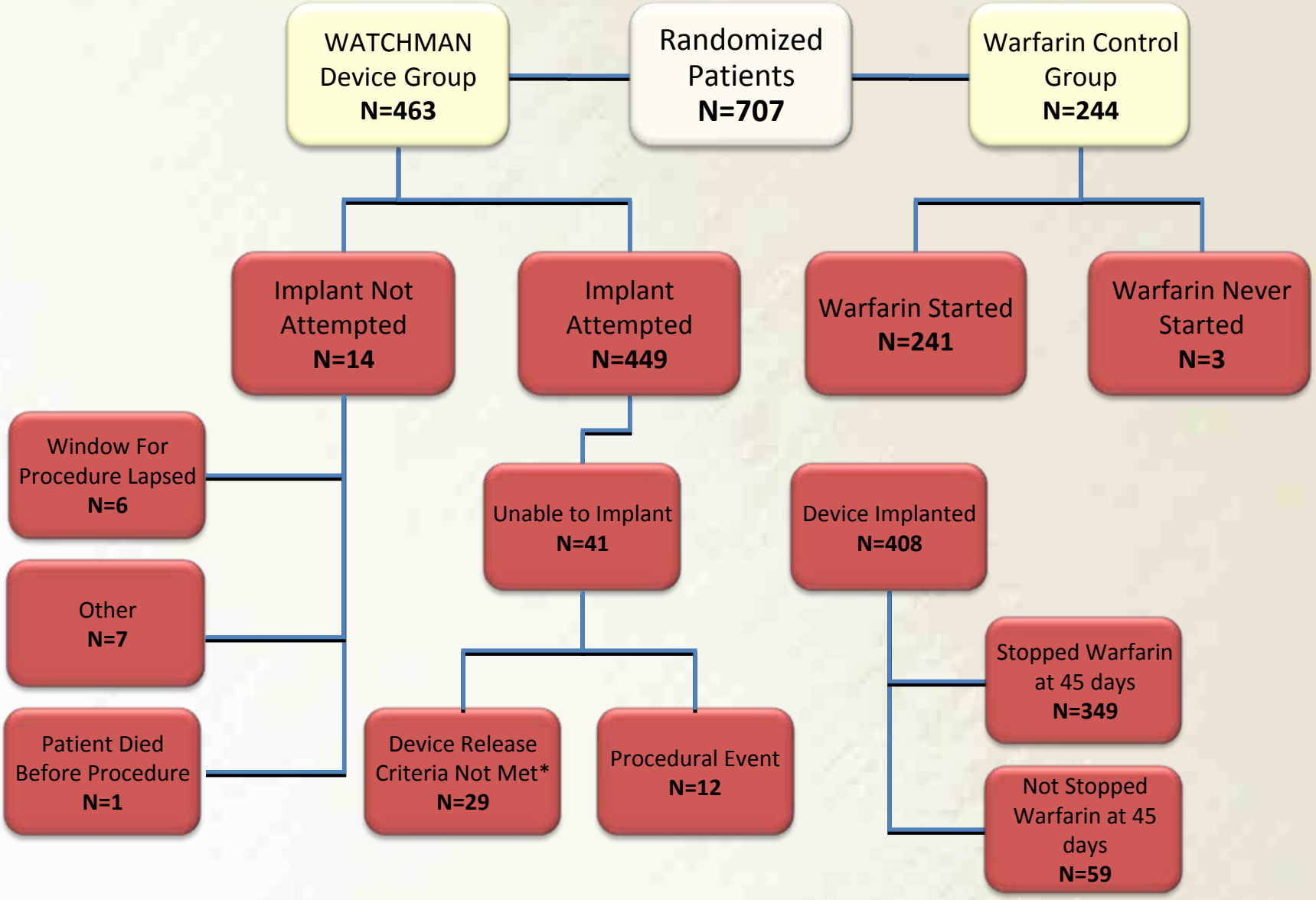
✓ Key Inclusion Criteria

- Age 18 years or older
- Documented non-valvular AF
- Eligible for long-term warfarin therapy, and no other conditions that would require long-term warfarin therapy
- Calculated CHADS2 score $\geq$ 1

✓ Key Exclusion Criteria

- NYHA Class IV Congestive Heart Failure
- ASD and/or atrial septal repair or closure device
- Planned ablation procedure within 30 days of potential WATCHMAN Device implant
- Symptomatic carotid disease
- LVEF < 30%
- TEE Criteria: Suspected or known intracardiac thrombus (dense spontaneous echo contract)

PROTECT AF Enrollment Summary



PROTECT AF Trial Endpoints

- ✓ Primary Efficacy Endpoint
  - All stroke: ischemic or hemorrhagic
    - deficit with symptoms persisting more than 24 hours or
    - symptoms less than 24 hours confirmed by CT or MRI
  - Cardiovascular and unexplained death: includes sudden death, MI, CVA, cardiac arrhythmia and heart failure
  - Systemic embolization
- ✓ Primary Safety Endpoint
  - Device embolization requiring retrieval
  - Pericardial effusion requiring intervention
  - Cranial bleeds and gastrointestinal bleeds
  - Any bleed that requires ≥ 2uPRBC

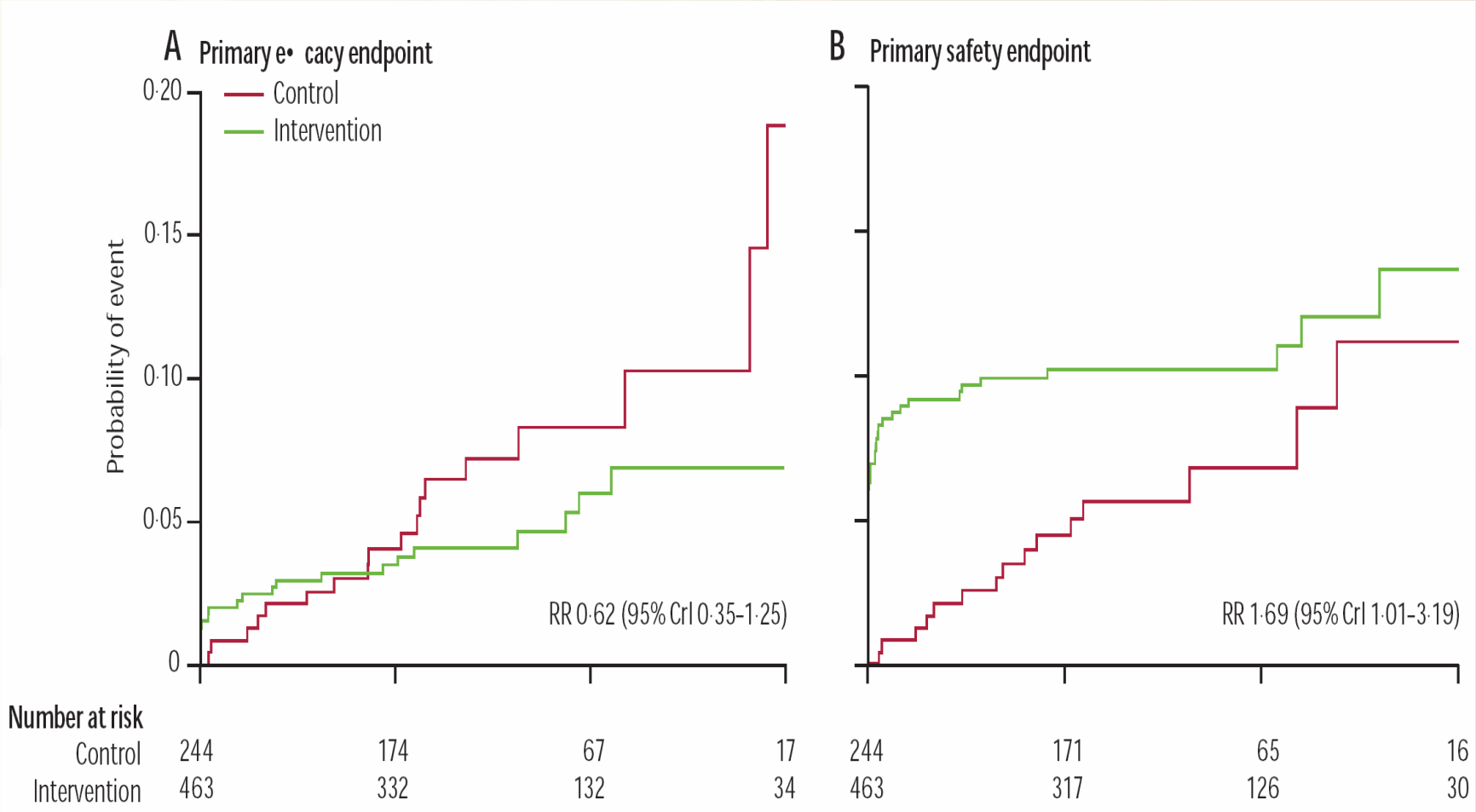
Results

- ✓ At the pre-specified 45-day followup, 86% of the device patients had a TEE that met the pre-defined criteria necessary to discontinue warfarin
- ✓ After stopping warfarin, participants with the device were prescribed clopidogrel 75 mg daily and aspirin 81 mg daily. The clopidogrel was stopped after the 6-month follow-up visit
- ✓ After a mean follow-up of 18 months, the primary efficacy rate of stroke (including ischemic or hemorrhagic), cardiovascular or unexplained death, or systemic embolism was:
  - 3.0 per 100 patient-years in the intervention group and 4.9 per 100 patient-years in the control group
  - The probability of noninferiority to warfarin was 99.9% based on a 2-fold noninferiority margin

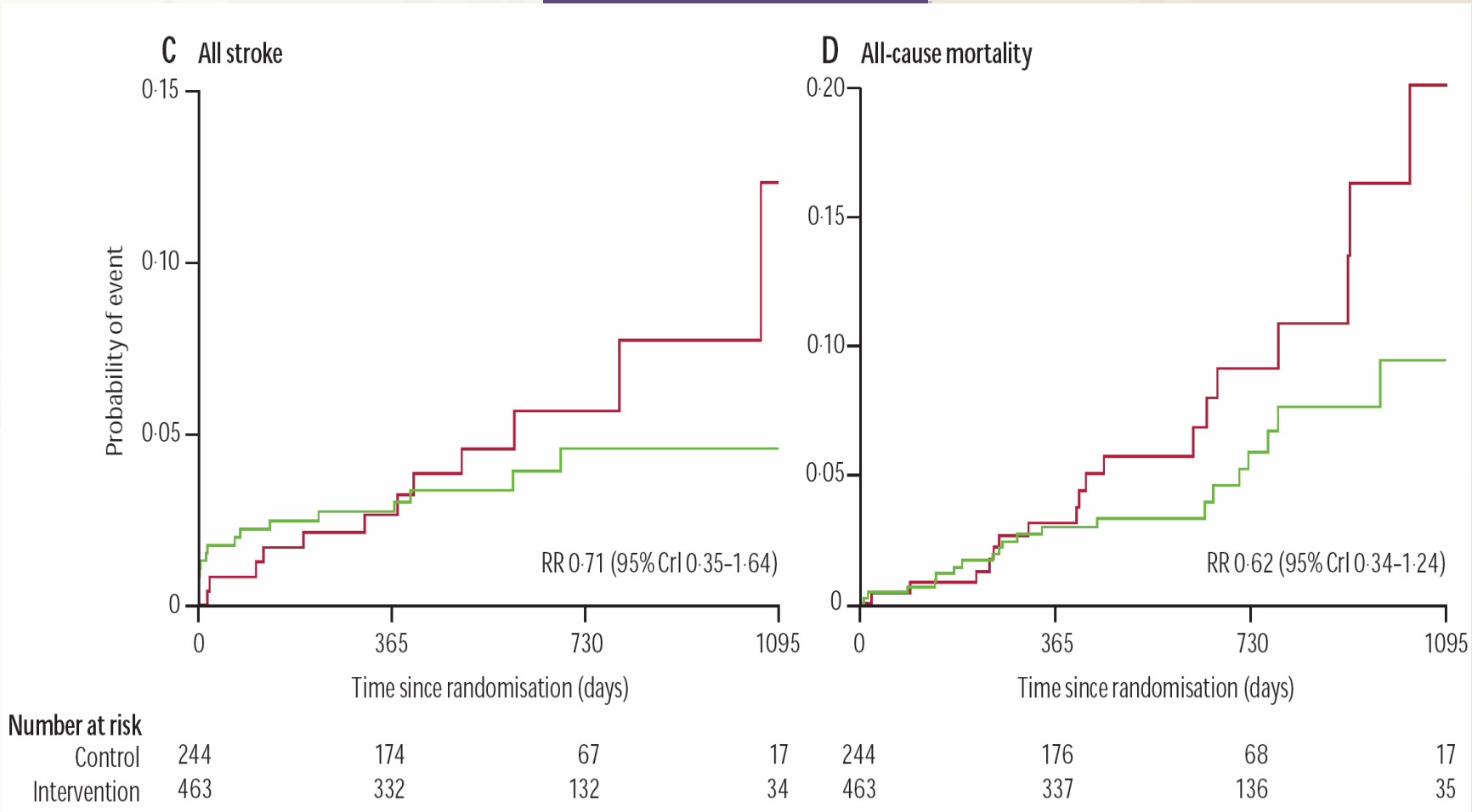
Results

- ✓ When the analysis was restricted to only those in the intervention group who had successful device implantation allowing for warfarin discontinuation, the device was found to be superior for this primary efficacy end point (RR=0.40)
- ✓ Ischemic strokes were more common in the intervention group, and hemorrhagic strokes were more common in the warfarin group
- ✓ Complications of the device implant procedure included:
  - serious pericardial effusion in 22 (4.8%)
  - procedure-related ischemic stroke attributed to air embolism in 5 (1.1%)
  - and device embolization in 3 (0.6%)
- ✓ There were no deaths related to the closure device

RESULTS - Primary efficacy endpoint and Primary safety endpoint

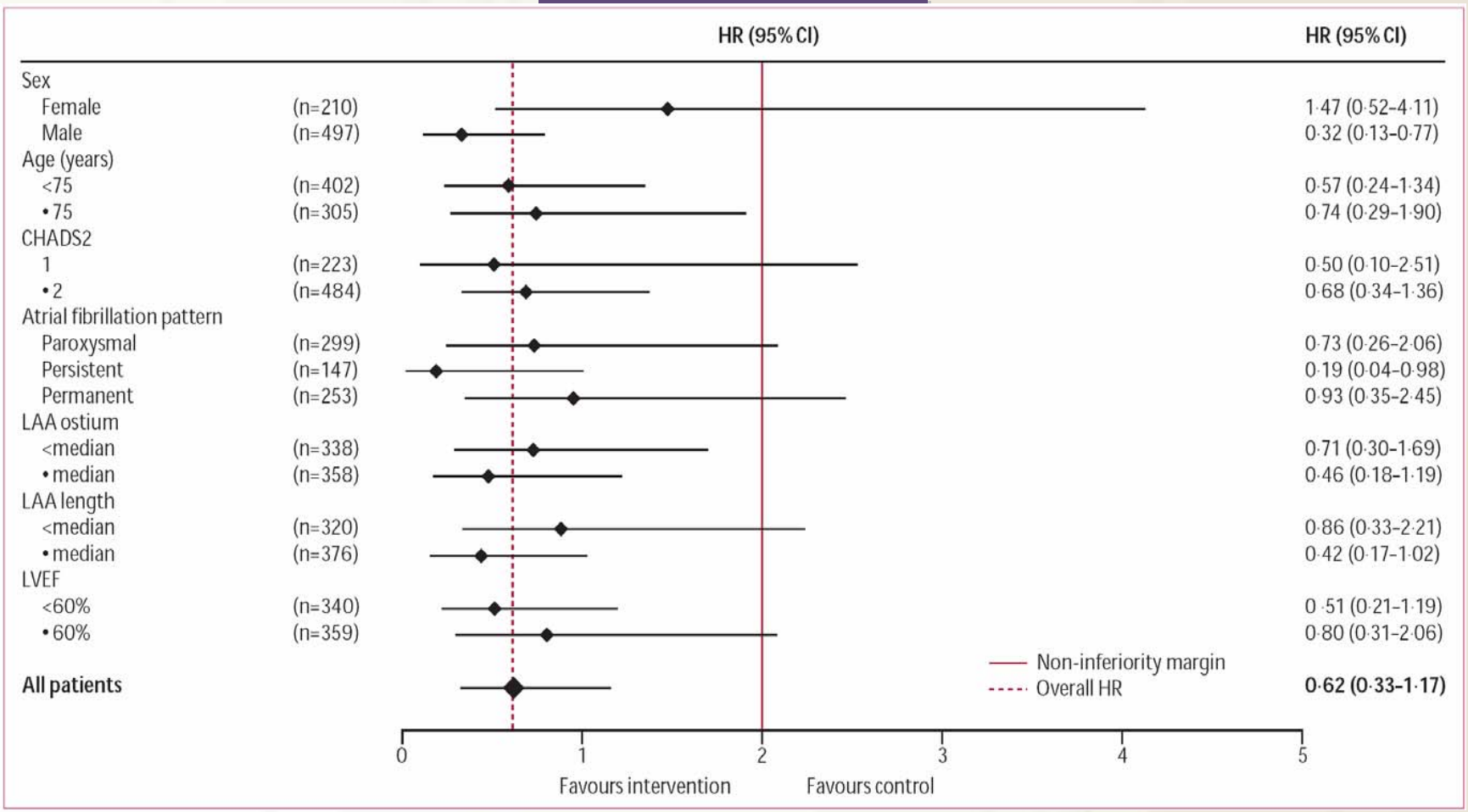


RESULTS – All stroke and All-cause mortality



Number at risk								
Control	244	174	67	17	244	176	68	17
Intervention	463	332	132	34	463	337	136	35

Primary efficacy results by patient subgroup



Adverse events

	Intervention (n=463)	Control (n=244)
Serious pericardial e• usion*	22 (4·8%)	0
Major bleeding†	16 (3·5%)	10 (4·1%)
Procedure-related ischaemic stroke	5 (1·1%)	0
Device embolisation	3 (0·6%)	0
Haemorrhagic stroke‡	1 (0·2%)	6 (2·5%)
Other§	2 (0·4%)	0

*Defined as the need for percutaneous or surgical drainage. †Major bleeding is defined as a bleeding event that required at least 2 units of packed red blood cells or surgery to correct. ‡Of the seven haemorrhagic strokes, six resulted in death (intervention group, n=1; control group, n=5). §An oesophageal tear and a procedure-related arrhythmia.

Table • : Adverse events

Summary

- ✓ PROTECT AF provides good evidence that a percutaneously placed LAA occlusion device might be a reasonable alternative to warfarin in patients with AF and additional stroke risk factors
- ✓ The fact that those with successful closure fared better than those assigned to warfarin is proof of principle that the LAA is indeed the culprit in the majority of strokes due to AF
- ✓ Several important limitations of the study:
  - substantial learning curve associated with device implantation
  - 10% of device patients who had discontinued warfarin restarted it for clinical reasons
  - the finding of thrombus formation on the device in 15 patients despite the prescribed warfarin and antiplatelet therapy

Summary

- ✓ Long-term warfarin treatment of patients with AF has been found effective, but presents difficulties and risk
- ✓ PROTECT AF trial was a randomized, controlled, statistically valid study to evaluate the WATCHMAN device compared to warfarin
- ✓ In PROTECT AF, hemorrhagic stroke risk is significantly lower with the device.
  - When hemorrhagic stroke occurred, risk of death was markedly increased
- ✓ In PROTECT AF, all cause stroke and all cause mortality risk are non-inferior to warfarin
- ✓ In PROTECT AF, there are early safety events, specifically pericardial effusion; these events have decreased over time

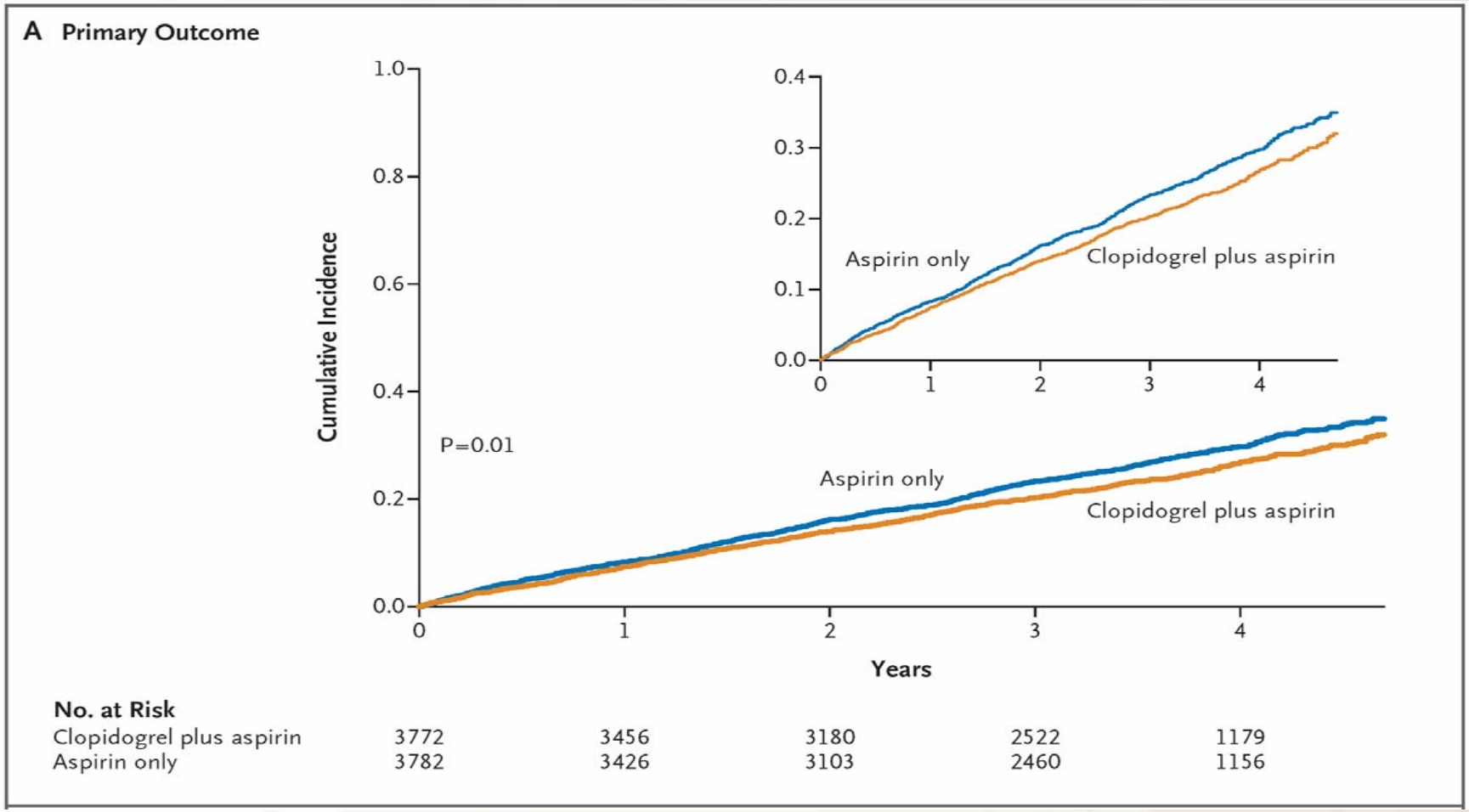
Effect of Clopidogrel Added to Aspirin in Patients with AF (The ACTIVE Study, N Engl J Med 2009;360:2066-78)

- ✓ The ACTIVE W trial previously showed that combination aspirin and clopidogrel was inferior to warfarin in stroke prevention in patients with AF
- ✓ ACTIVE A enrolled 7,554 AF patients with at least 1 additional risk factor for stroke who were felt to be unsuitable for warfarin therapy
- ✓ They were randomized to clopidogrel at 75 mg/day versus placebo in a double-blind fashion
- ✓ All patients also received aspirin at a recommended dose of 75 to 100 mg/day

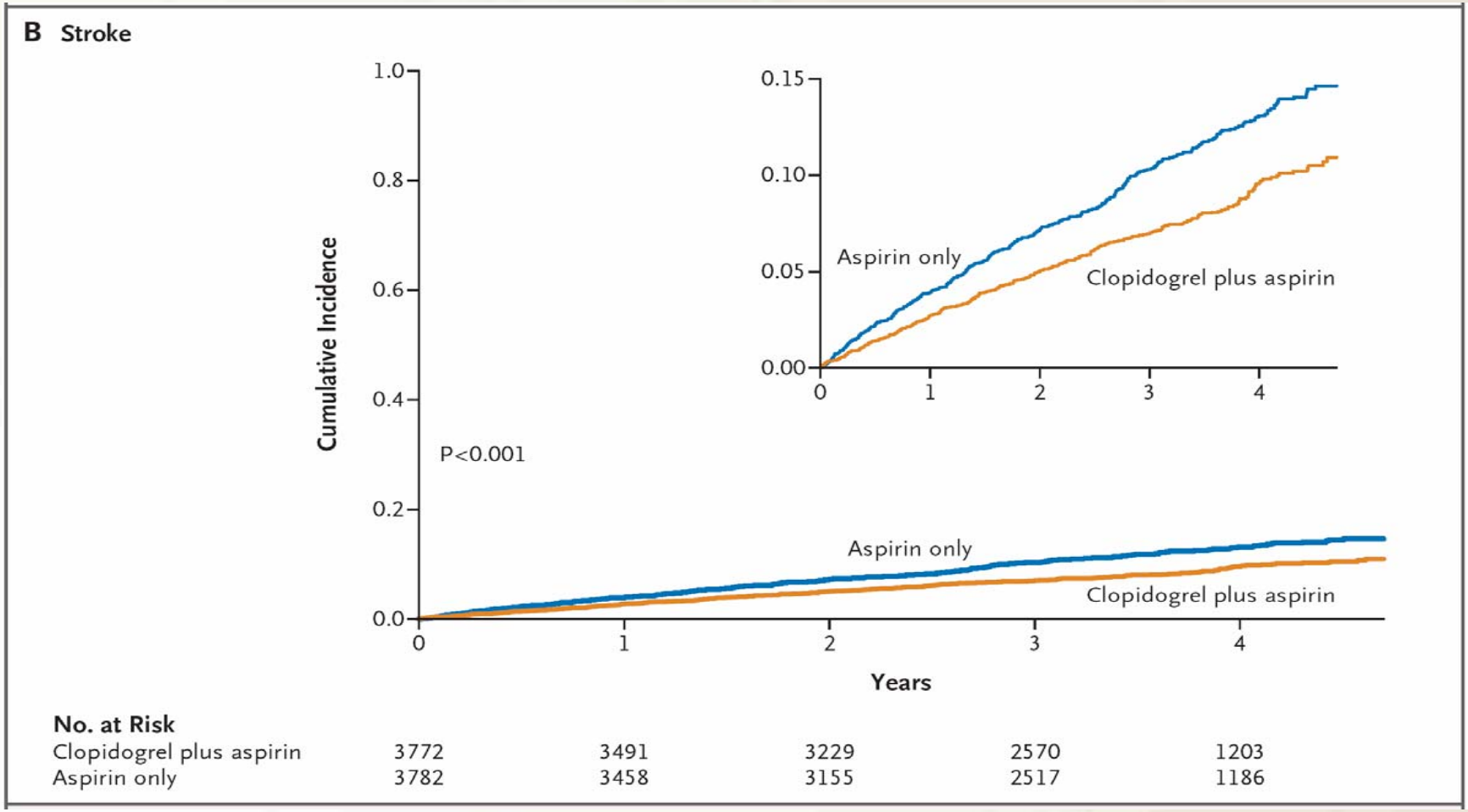
RESULTS

- ✓ The primary outcome of any major vascular event (stroke, non-central nervous system embolism, myocardial infarction, or death from vascular causes) was:
  - 6.8% per year in the clopidogrel group versus 7.6% per year in the placebo group (RR=0.89, $p<0.01$)
- ✓ This benefit was primarily due to a decrease in stroke
- ✓ Patients in the clopidogrel group experienced major bleeding significantly more frequently than those in the placebo group (RR=1.57, $p<0.001$)

RESULTS


A Primary Outcome
Cumulative Incidence
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
Years
P=0.01
Aspirin only
Clopidogrel plus aspirin
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
Aspirin only
Clopidogrel plus aspirin
No. at Risk
Clopidogrel plus aspirin 3772 3456 3180 2522 1179
Aspirin only 3782 3426 3103 2460 1156

RESULTS


B Stroke
Cumulative Incidence
1.0
0.8
0.6
0.4
0.2
0.0
P<0.001
Aspirin only
Clopidogrel plus aspirin
0.15
0.10
0.05
0.00
0
1
2
3
4
Years
No. at Risk
Clopidogrel plus aspirin 3772 3491 3229 2570 1203
Aspirin only 3782 3458 3155 2517 1186

RESULTS

Table 3. Relative Risks of Hemorrhage, According to Treatment Group.

Bleeding	Clopidogrel plus Aspirin		Aspirin		Relative Risk (95% CI)	P Value
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Major bleeding	251	2.0	162	1.3	1.57 (1.29–1.92)	<0.001
Severe	190	1.5	122	1.0	1.57 (1.25–1.98)	<0.001
Fatal	42	0.3	27	0.2	1.56 (0.96–2.53)	0.07
Minor bleeding	408	3.5	175	1.4	2.42 (2.03–2.89)	<0.001
Any bleeding	1014	9.7	651	5.7	1.68 (1.52–1.85)	<0.001
Site of major bleeding*						
Gastrointestinal	132	1.1	68	0.5	1.96 (1.46–2.63)	<0.001
Gastrointestinal, with transfusion	117	0.9	61	0.5	1.93 (1.42–2.63)	<0.001
Intracranial	54	0.4	29	0.2	1.87 (1.19–2.94)	0.006
Extracranial	200	1.6	134	1.1	1.51 (1.21–1.88)	<0.001

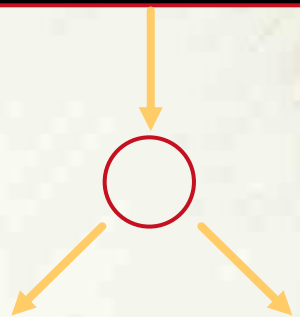
Summary

- ✓In sum, clopidogrel plus aspirin appears to be superior to aspirin alone in preventing stroke in the setting of AF, but at a cost of more bleeding
- ✓The benefit is somewhat incremental, but may be worthwhile in a patient deemed to be unsuitable for warfarin

ATHENA - Effect of Dronedarone on Cardiovascular vents in Atrial Fibrillation (N Engl J Med 2009;360:668-78)

Qualifying patients with paroxysmal / persistent AF:

- Age ≥ 75 years with / without additional risk factors
- Age ≥ 70 years and ≥ 1 risk factor (hypertension; diabetes; prior stroke / TIA; LA ≥ 50 mm; LVEF ≤ 0.40)



> 80% OF PTS IN BOTH GROUPS ON RATE CONTROL Rx

Dronedarone 400 mg BID

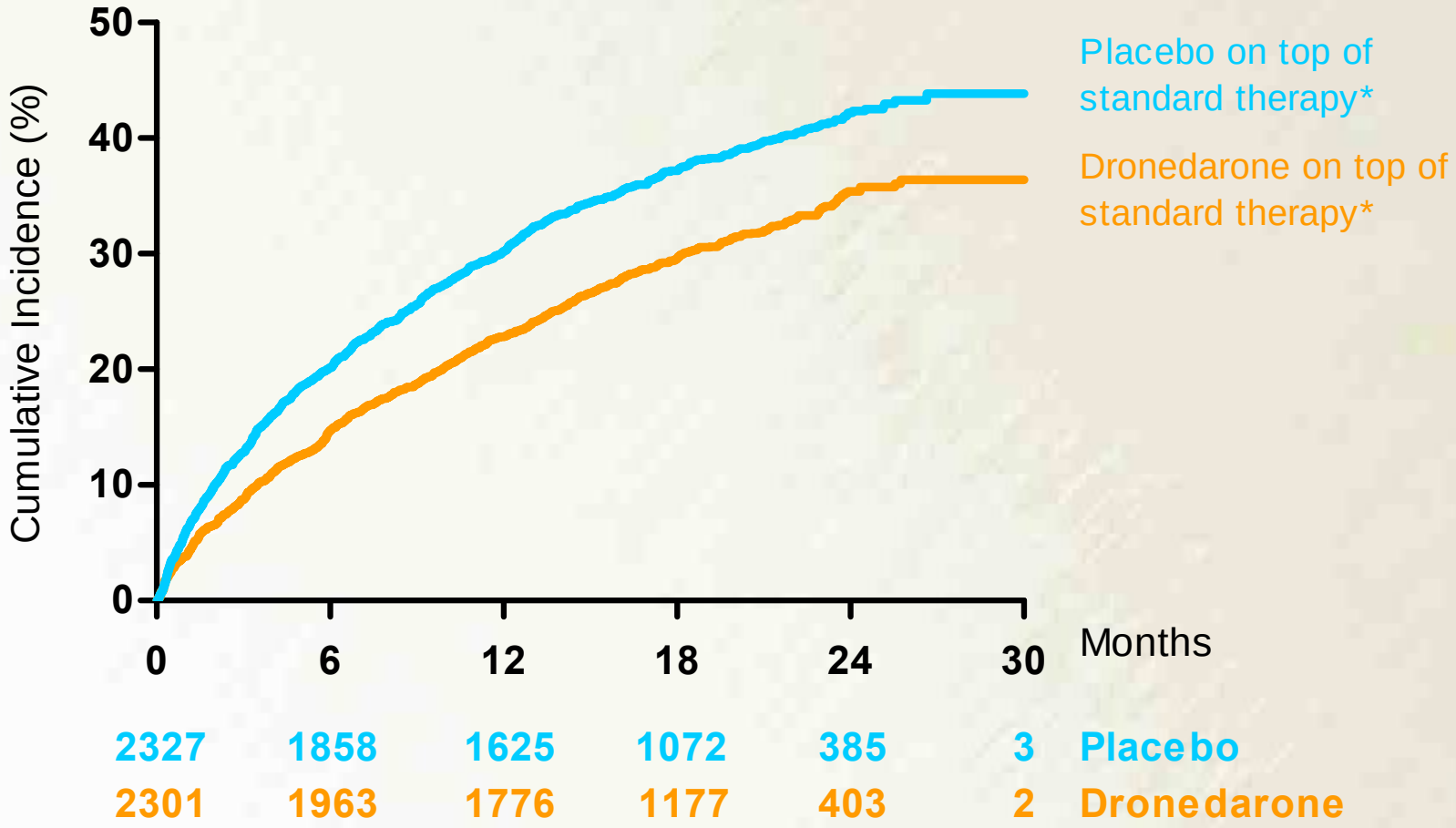
Placebo

Minimum follow-up 12 months

ATHENA

- ✓ **The primary outcome was:**
  - the first hospitalization due to cardiovascular events
  - or death
- ✓ **The secondary outcomes were:**
  - death from any cause
  - death from cardiovascular causes
  - and hospitalization due to cardiovascular events

Primary Outcome – Death or Cardiovascular Hospitalization



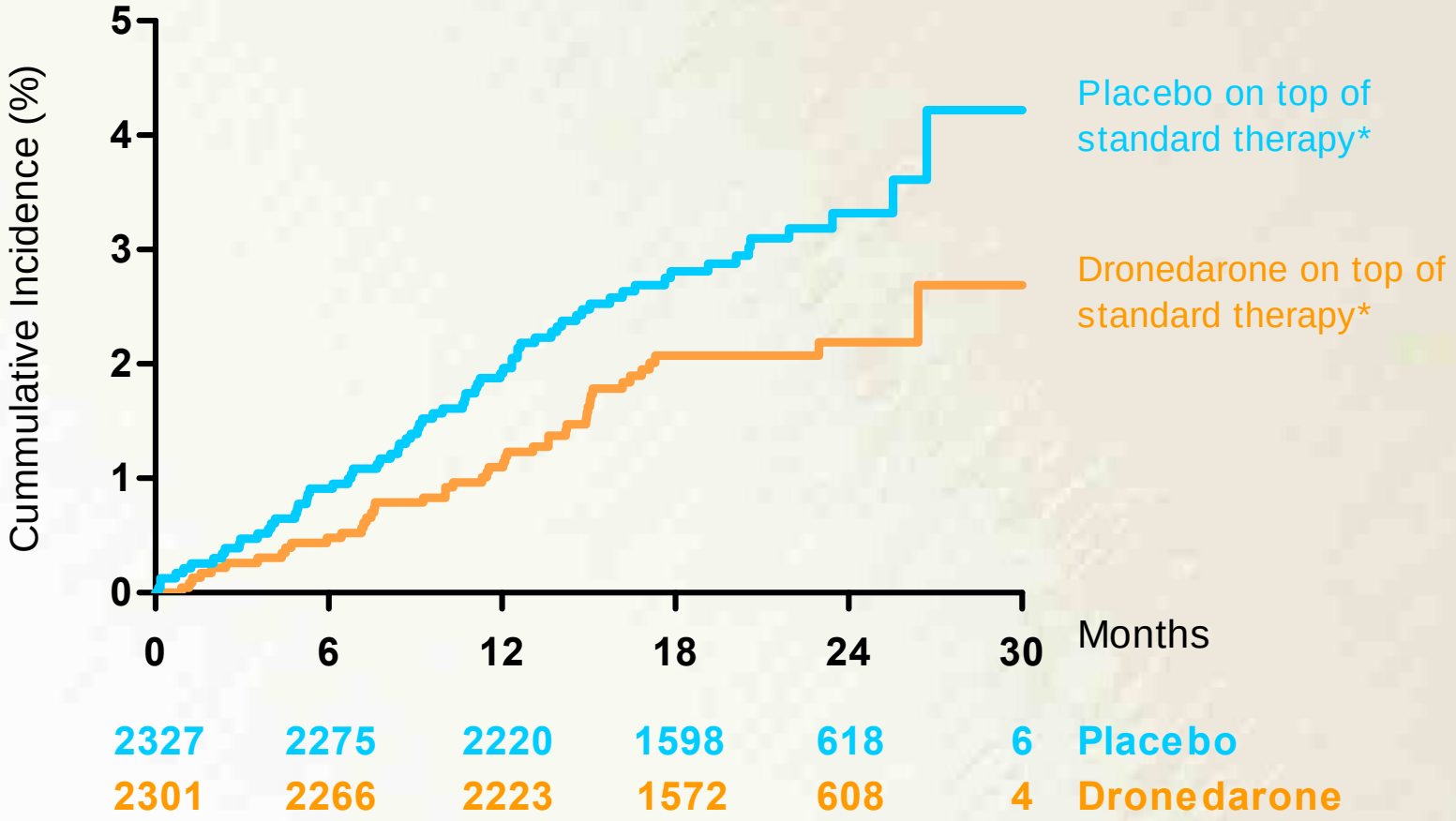
Analysis of Stroke in ATHENA

(*Circulation*. 2009;120:1174-1180.)

- ✓ In ATHENA, there were:
  - 70 strokes with placebo (1.8% per year)
  - 46 strokes with dronedarone (1.2% per year)

  RR=0.66, p<0.027
- ✓ The Kaplan-Meier curves were noted to separate early and remain that way throughout the study
- ✓ The stroke outcomes were not pre-specified
- ✓ The investigators did not report whether this reduction in stroke was mediated by a reduction in AF
- ✓ Of note, those receiving dronedarone exhibited a trend toward lower SBP and a significant reduction in DBP compared with placebo, suggesting that the antihypertensive effect may have contributed to the lower rate of stroke

STROKE


Cummulative Incidence (%)
5
4
3
2
1
0
0
6
12
18
24
30
Months
Placebo on top of standard therapy*
Dronedarone on top of standard therapy*
2327 2275 2220 1598 618 6 Placebo
2301 2266 2223 1572 608 4 Dronedarone

Comments

- ✓ The majority of strokes occurred in those who either were not undergoing vitamin K antagonist therapy or in whom the INR ratio was subtherapeutic
- ✓ Particularly important in interpreting this study is the fact that stroke outcomes were not pre-specified
- ✓ Instead, information regarding stroke was gathered from hospitalization reports and death reports
- ✓ Approximately 60% of all participants were receiving VKA therapy at baseline, and this was well balanced between the groups

Mechanisms by which dronedarone could reduce the risk of stroke

- ✓ The most likely mechanism is by suppression of AF
  - Dronedarone reduce AF by 25% in previous studies and also in ATHENA
  - However, There was a trend for reduction in stroke even in patients who appeared to be in AF
- ✓ Dronedarone, cause a modest reduction in BP in ATHENA
  - Small reductions in BP have been reported to have a significant impact on stroke
- ✓ Hart rate slowing during AF with dronedarone
  - Recently, the ERATO trial in patients with permanent AF
    - 12-bpm reduction in HR at rest
    - and a 25-bpm reduction during exercise
  - These rate-slowing effects were additive to those of other rate control agents
  - It is possible that a slower rate during AF recurrence could directly reduce the risk of stroke by preventing hypotension

Comparison of AAD Therapy and RF Catheter Ablation in Patients With PAF (ThermoCool AF trial)

(JAMA. 2010;303(4):333-340)

- ✓ ThermoCool AF trial, a prospective, multicenter, randomized (2:1) trial comparing open irrigated catheter ablation (n=106) with antiarrhythmic drug therapy (n=61)
- ✓ Enrollment required:
  - at least 3 symptomatic AF episodes in the last 6 months
  - and failure to respond to at least 1 AAD
- ✓ In addition to follow-up at for symptoms of AF, all participants were required to transmit symptomatic episodes using transtelephonic Monitoring
- ✓ For the ablation procedure, pulmonary vein isolation confirmed by entrance block was required,
- ✓ Although repeat ablation procedures were allowed, the primary results reflected outcomes after a mean 1.1 procedures per patient

ThermoCool AF trial

- ✓ For those assigned to the drug arm, the choice of drug was at the discretion of the investigator
- ✓ The majority in the drug arm received either flecainide or Propafenone
- ✓ A 3-month blanking period was in place after catheter ablation in the ablation arm, and a 14-day blanking period was in place during titration of medicines in the drug arm, during which efficacy was not assessed

End points

- ✓ The primary end point was freedom from protocol-defined treatment failure, which included:
  - documented symptomatic PAF during the effectiveness evaluation period
  - Patients in the ablation group with:
    - repeat ablation after day 80 after the initial ablation
    - absence of entrance block confirmed in all PVs at the end of the ablation procedure
  - changes in specified drug regimen postblanking including:
    - class I/III drugs
    - ACE inhibitors
    - ARB
    - atrioventricular nodal blocker

    Were also considered treatment failures, even if they remained free from symptomatic PAF
  - In the AAD group, an adverse event requiring discontinuation of the assigned drug was also considered a treatment failure

Secondary end points

- ✓ Freedom from symptomatic atrial arrhythmia (AF, atrial tachycardia, atrial flutter),
- ✓ Freedom from any atrial arrhythmia (symptomatic or asymptomatic)
- ✓ QOL outcomes
  - – Instruments used to evaluate QOL included:
    - Short-Form Health Survey (SF-36), Version 2
    - and the AF Symptom Frequency and Severity Checklist

Safety Outcomes

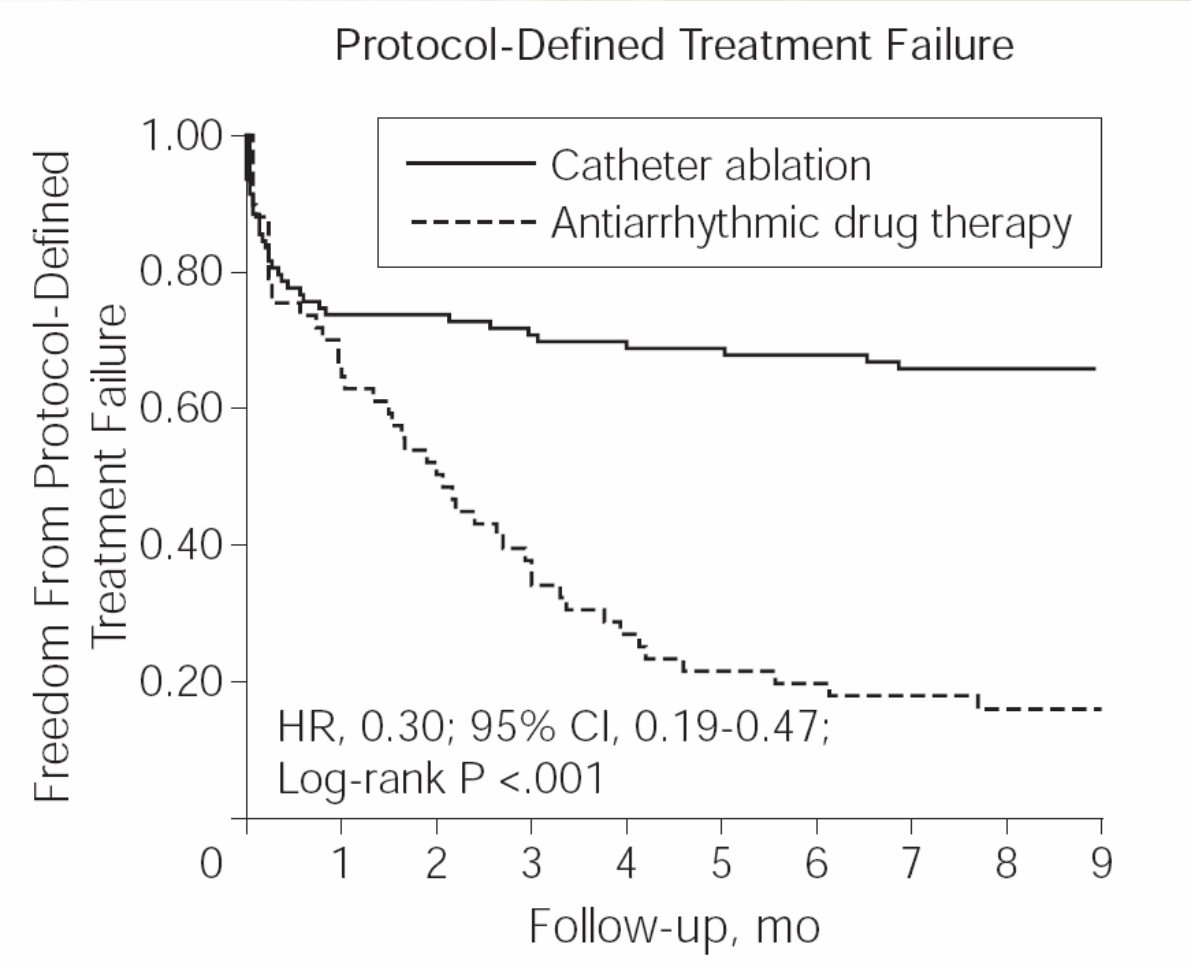
- ✓ Major treatment-related adverse events were defined as those that occurred within 30 days of the ablation procedure or within 30 days following initiation of drug therapy

- ✓ Prespecified major adverse events included
  - death, myocardial infarction, PV stenosis,
  - diaphragmatic paralysis, atrio-esophageal fistula
  - transient ischemic attack, thromboembolic events
  - pericarditis, cardiac tamponade, pericardial effusion
  - pneumothorax, vascular access complications, pulmonary edema
  - congestive heart failure, heart block, life-threatening ventricular arrhythmias
  - and intolerance to assigned AAD requiring discontinuation

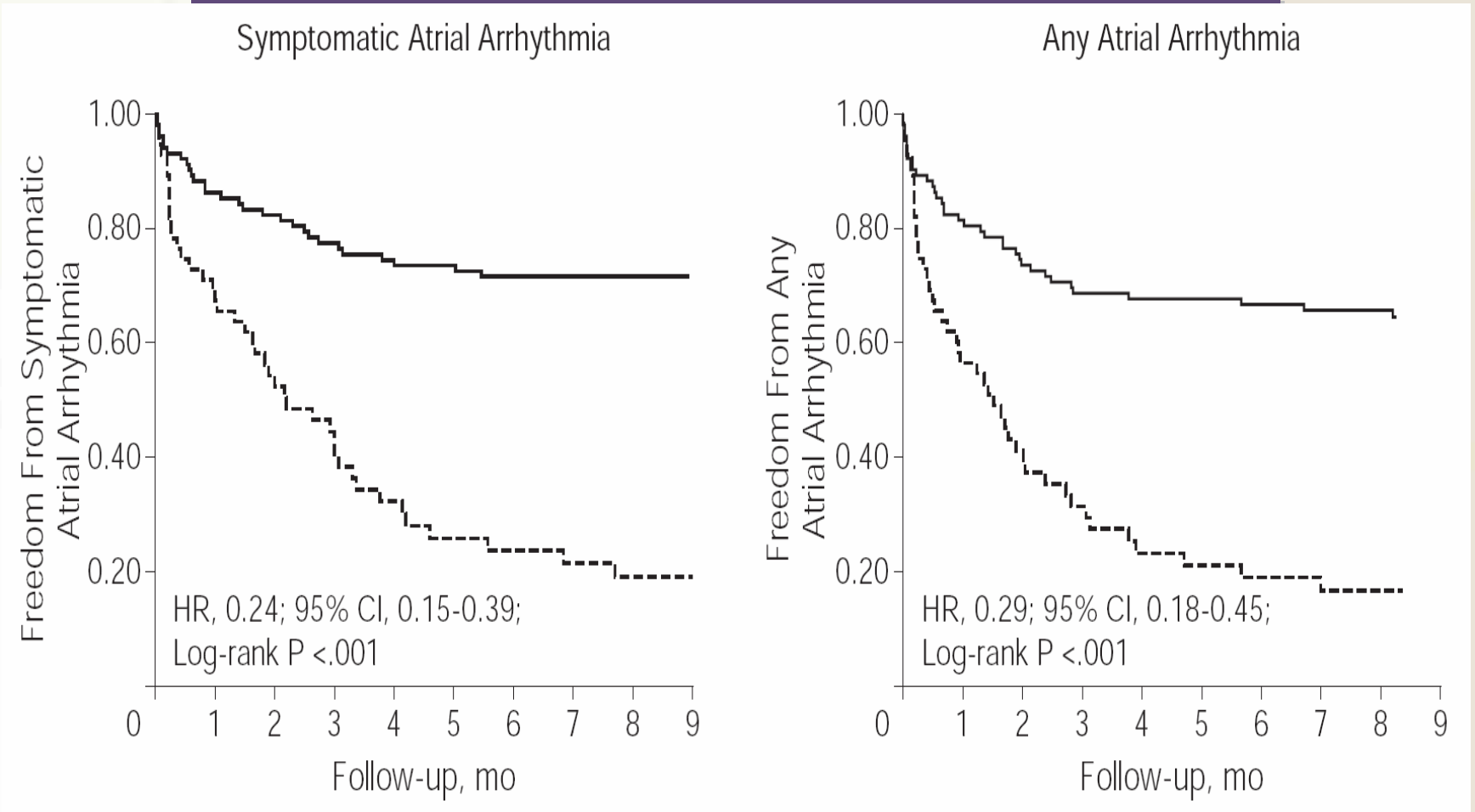
RESULTS

- ✓ The primary end point of freedom from protocol-defined treatment failure
  - was 66% in the catheter ablation group
  - and 16% in the AAD group (HR=0.30, p<0.001)
- ✓ The quality of life improved significantly in the ablation group compared with the AAD group
- ✓ Thirty-day major treatment-related adverse events occurred:
  - in 5 patients (5%) in the ablation group (1 pericardial effusion, 1 pulmonary edema, 1 pneumonia, 1 vascular complication, and 1 heart failure [HF])
  - and in 5 patients (9%) in the drug group (2 life-threatening arrhythmias and 3 with drug intolerance requiring discontinuation)

Protocol-Defined Treatment Failure



Symptomatic Atrial Arrhythmia and Any Atrial Arrhythmia



Comments

- ✓ The ThermoCool AF trial demonstrate superior efficacy in preventing symptomatic recurrent AF with RF ablation

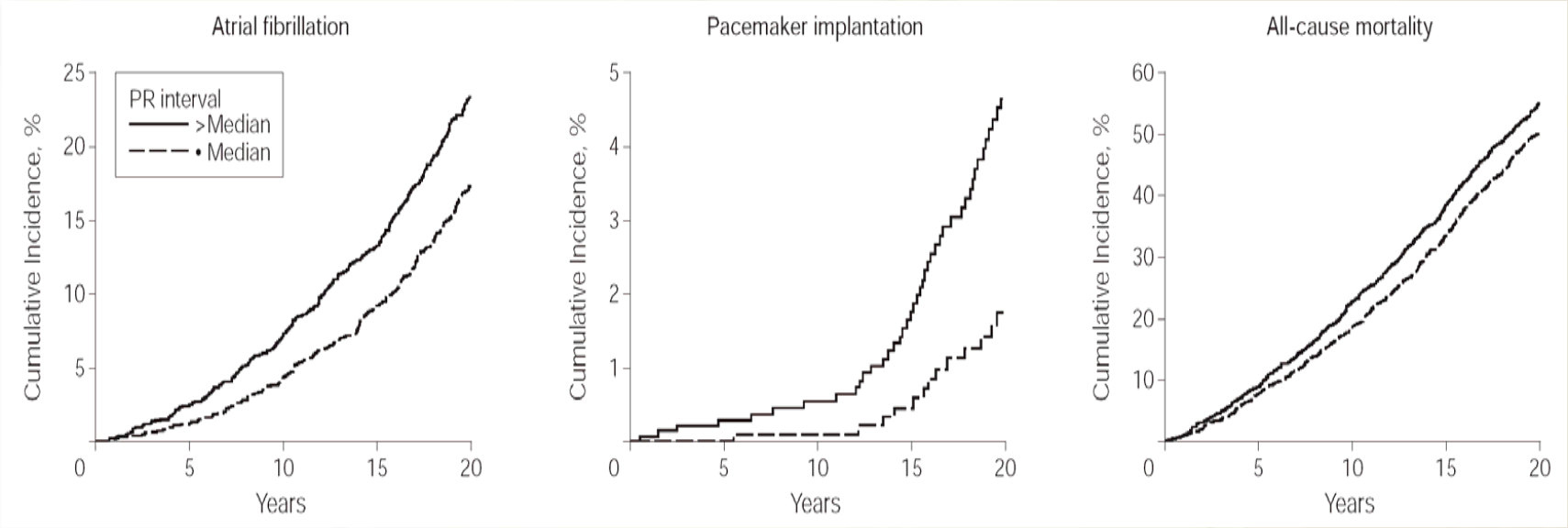
- ✓ There are a few caveats to bear in mind:
  - Although this is the most rigorous, multicenter catheter ablation trial done to date, the centers involved were generally quite experienced in the procedure. The findings may therefore not apply to all centers
  - Those who failed drug therapy may represent patients who are destined to do poorly on drug treatment
  - Although the 3-month blanking period after ablation is reasonable, this did result in less follow-up time for those undergoing ablation
  - In addition, some evidence suggests that, over time, late AF recurrence may return, therefore, this 9-month efficacy end point (and mean follow-up of 12.5 months) may not be sufficient to teach us about long-term results

Long-term Outcomes in Individuals With Prolonged PR Interval or First-Degree AVB (JAMA. 2009;301(24):2571-2577)

- ✓ Using data from the Framingham Heart Study, investigators examined the PR interval in 7,575 individuals as a predictor of:
  - incident AF
  - pacemaker implantation
  - and mortality
- ✓ Dichotomizing the PR interval into 200 ms or not (i.e., first-degree heart block or not)

RESULTS

- ✓ They found that first-degree heart block was associated with:
  - an unadjusted HR of 4.26 (95% CI: 2.85 to 6.38) for AF
  - 10.26 (95% CI: 6.66 to 15.82) for pacemaker implantation
  - 2.72 (95% CI: 2.11 to 3.51) for all-cause mortality



RESULTS

- ✓ After multivariable adjustment, an increasing PR interval was associated with an increased risk for each of these outcomes
- ✓ Similar results were observed after excluding individuals taking nodal blocking medications

Table 4. First-Degree Atrioventricular Block and Risks of Atrial Fibrillation, Pacemaker Implantation, and All-Cause Mortality[a]

	HR (95% CI)							
	All				No Nodal-Blocking Medications			
End Point	Unadjusted	P Value	Multivariable-Adjusted	P Value	Unadjusted	P Value	Multivariable-Adjusted	P Value
Atrial fibrillation[b]	4.26 (2.85-6.38)	• .001	2.06 (1.36-3.12)	• .001	4.91 (3.23-7.48)	• .001	2.36 (1.53-3.64)	• .001
Pacemaker implantation[c]	10.26 (6.66-15.82)	• .001	2.89 (1.83-4.57)	• .001	13.30 (7.76-22.80)	• .001	4.32 (2.46-7.59)	• .001
All-cause mortality[d]	2.72 (2.11-3.51)	• .001	1.44 (1.09-1.91)	.01	2.86 (2.18-3.76)	• .001	1.48 (1.10-1.99)	.01

Comments

- ✓There are several potential mechanisms that might be responsible:
  - a longer PR interval may be due to atrial fibrosis and decreased atrial conduction time
  - Or, it might reflect general fibrosis, affecting both the conduction system and the atria
  - It may also reflect greater vagal tone, which might also be responsible for AF
  - Finally, the long PR might itself have hemodynamic consequences that lead to AF

Ventricular Arrhythmias

- ✓ Incidence of and Outcomes Associated With VT/F in Patients Undergoing PCI (*JAMA. 2009;301(17):1779-1789)*
- ✓ Long-Term Outcome Associated with Early Repolarization on ECG (N Engl J Med 2009;361:2529-37)
- ✓ Systematic Assessment of Patients With Unexplained Cardiac Arrest - Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER) (*Circulation*. 2009;120:278-285)

Incidence of and Outcomes Associated With VT/F in Patients Undergoing PCI *(JAMA. 2009;301(17):1779-1789)*

- ✓ The meaning of sustained VT or VF in the setting of a high-risk STEMI was studied as a secondary analysis of the APEX AMI (Assessment of Pexelizumab in Acute Myocardial Infarction) trial

- ✓ Of 5,745 acute high risk STEMI patients, sustained VT/VF occurred in 329 (5.7%)
  - 25 before cardiac catheterization
  - 180 during the cardiac catheterization
  - and 117 had the event after the procedure

- ✓ Ninety percent occurred within 48 h

Clinical Correlates of VT/VF

- ✓ Less VT/VF was associated with:
  - receiving beta-blockers
  - ACE inhibitors or ARB
  - or statins
- ✓ More often VT/VF was associated with:
  - those on class I and III antiarrhythmic drugs
  - receiving an intra-aortic balloon pump
  - undergoing repeat cardiac catheterization
  - undergoing dialysis
  - or requiring a blood transfusion

Clinical Correlates of VT/VF

- ✓ **Important predictors of either early or late VT/VF were:**
  - higher baseline heart rate
  - lower systolic blood pressure
  - higher baseline ST segment deviation
  - and lower pre-procedural TIMI flow grade

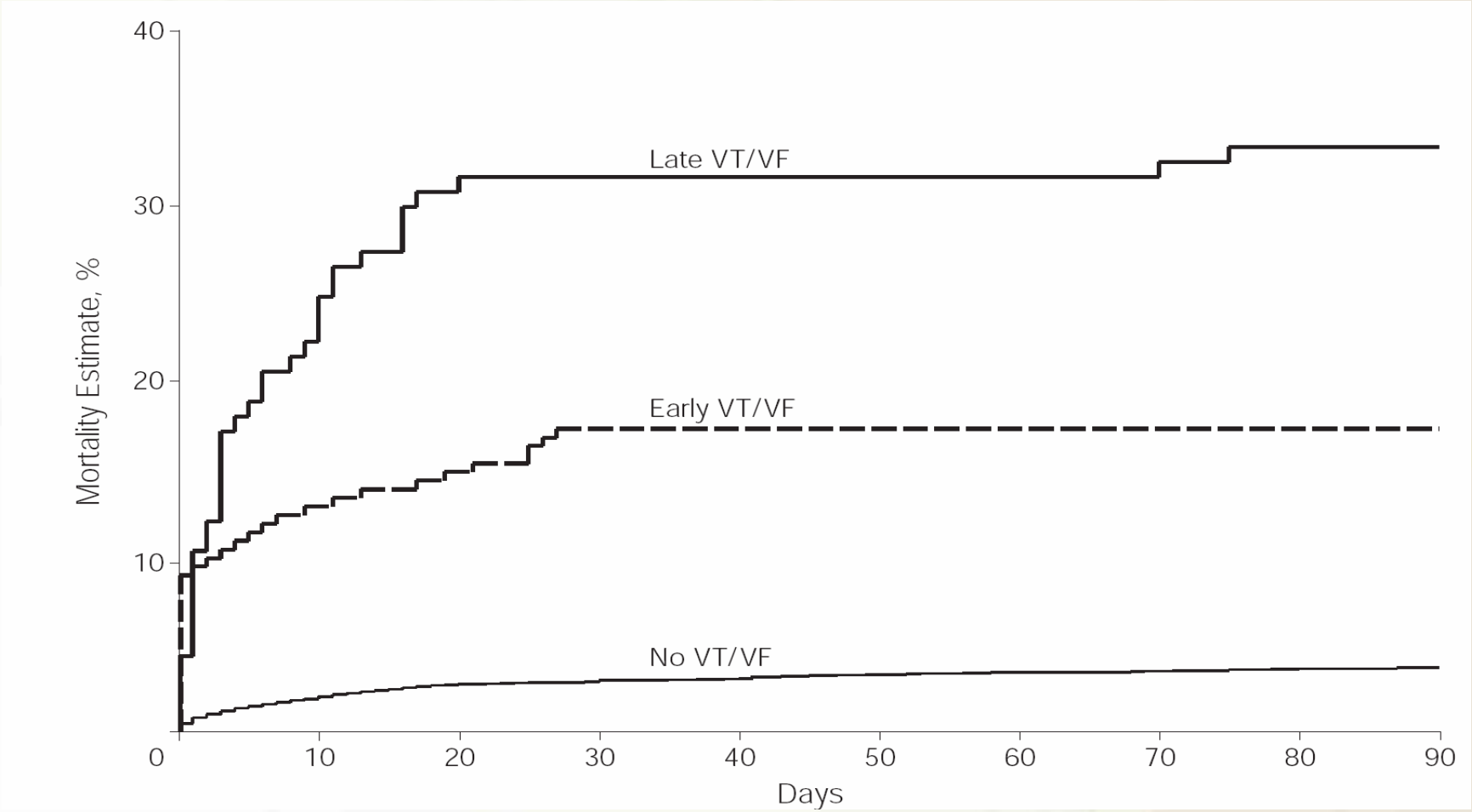
- ✓ **Predictors for early VT/VF were:**
  - Higher Killip class
  - inferior myocardial infarction
  - lower creatinine clearance
  - shorter time from symptom onset to randomization
  - and higher weight

- ✓ **Predictors for late VT/VF were:**
  - Post-procedural TIMI flow grade 3
  - lack of beta-blockers on admission
  - and ST-segment resolution<70%

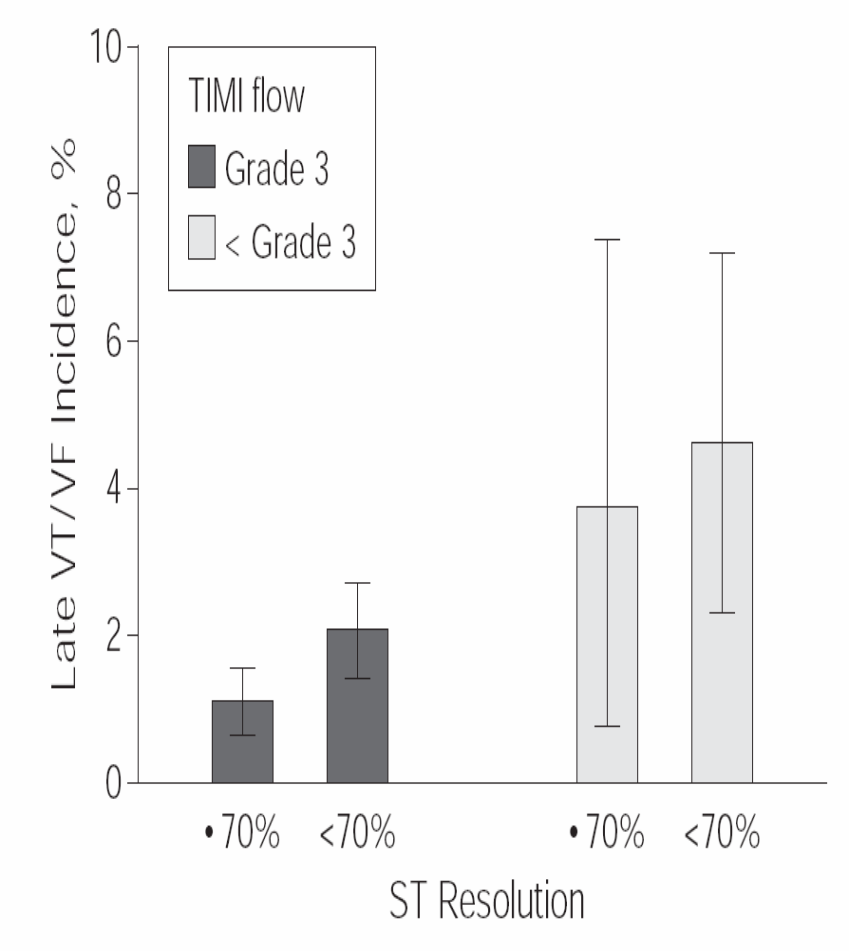
Mortality and VT/VF timing

- ✓ Mortality in those with any VT/VF was significantly higher than those without it (23.2% vs. 3.6%, HR: 7.33, 95% CI: 5.61 to 9.59)
- ✓ The excess mortality was:
  - mainly confined to the first 30 days
  - and was more common in those with late VT/VF
- ✓ After adjustment for potential confounders, VT/VF remained associated with a significant increase in mortality
- ✓ Of note, 70 (91%) of the deaths occurring in the VT/VF patients were cardiovascular, and of these, 30 (43%) were due to sudden cardiac death

Mortality and VT/VF timing

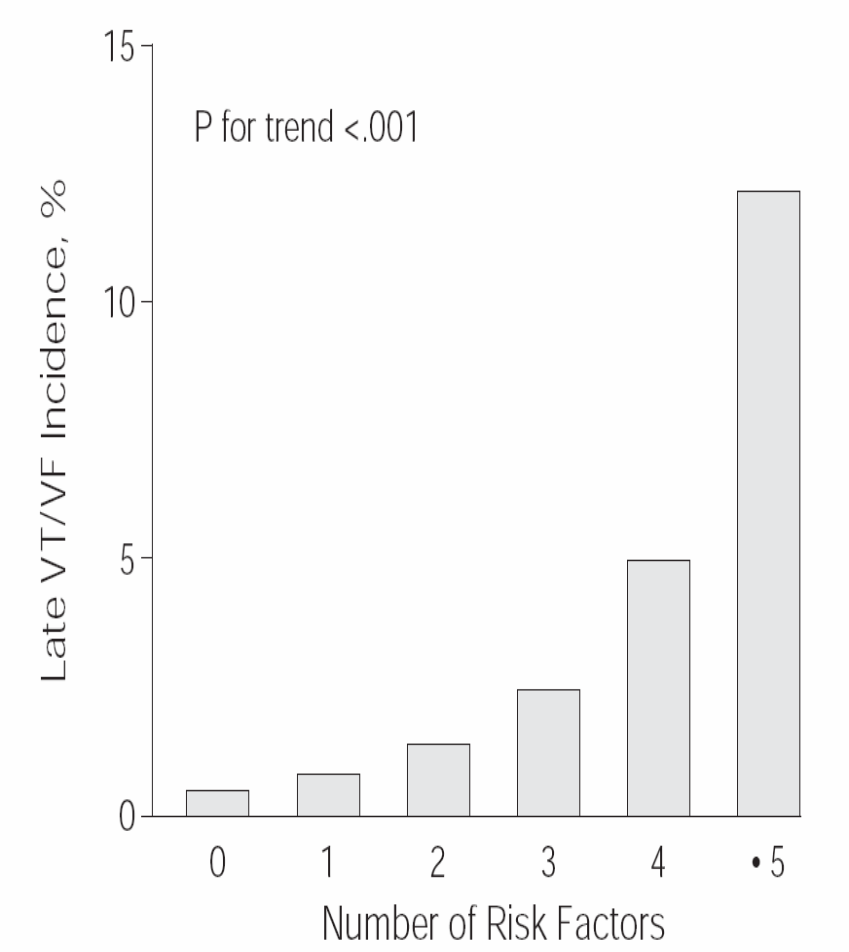


TIMI flow and ST elevation resolution



- ✓ Patients with late VT/VF were less likely to have post-procedural TIMI flow grade 3 and complete ST resolution (>70%) compared with those with early VT/VF
- ✓ The lowest incidence of late VT/VF occurred among patients with post-procedural TIMI flow grade 3 and complete ST resolution (>70%)
- ✓ The highest among those with post-procedural TIMI flow grade less than 3 and incomplete ST resolution

Risk Factor and VT/VF incidence



- ✓ Among patients with 2 or fewer risk factors (n=3484, two-thirds of study population), the incidence of late VT/VF was only 1.2%
- ✓ Even among patients with fewer than 3 risk factors (4726 patients, "90% of the patients), this incidence remained well under 2%

Comments

- ✓ Of interest, a similar proportion of those with no VT/VF had sudden death (36%, p=0.67)
- ✓ Therefore, the mechanism of death may be related to the generally sicker hearts and/or the conditions associated with more VT/VF
- ✓ It remains unknown whether the ventricular arrhythmia is causally related to worse outcomes or whether it simply reflects worse heart disease

Long-Term Outcome Associated with Early Repolarization on ECG (N Engl J Med 2009;361:2529-37)

- ✓ Recently, early repolarization or J-point elevation in the inferior and lateral leads has been shown to be more common in patients with idiopathic VF compared with controls

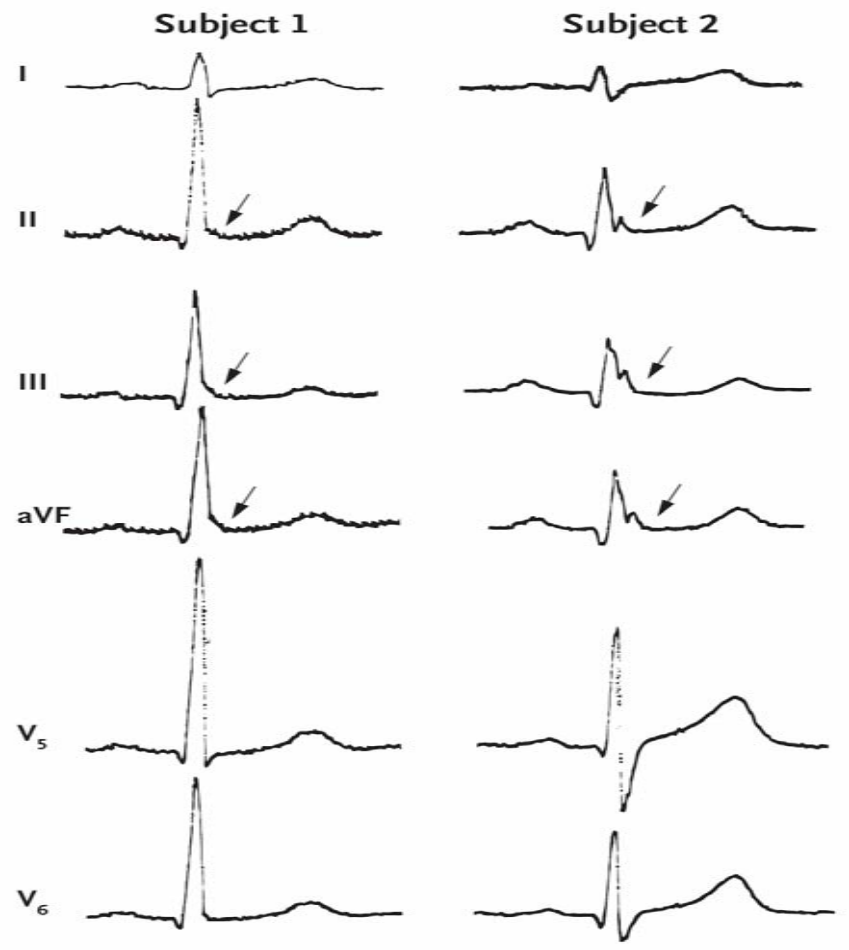
- ✓ Although the association appears to be quite strong, the risk of an adverse event when confronted with an asymptomatic patient with early repolarization remained unknown

- ✓ Investigators in Finland examined the baseline ECGs in 10,864 subjects in the Social Insurance Institution's Coronary Heart Disease Study that were obtained between 1966 and 1972

Early-repolarization patterns

- ✓ Early-repolarization patterns were sought in the inferior and lateral leads and stratified according to the degree of J-point elevation (≥0.1 or ≥0.2 mV) that was either notched or slurred in 2 consecutive leads
- ✓ The cause of death was determined by examining death certificates
- ✓ All deaths from a cardiac cause were then reviewed, including review of hospital records, to determine whether the death was likely associated with an arrhythmia or not

Early-repolarization patterns



- ✓ Baseline Electrocardiograms of Two Male Subjects with J-Point Elevation of More Than 0.2 mV in the Inferior Leads.
- ✓ In two subjects with J-point elevation of more than 0.2 mV in the inferior leads
- ✓ Subject 1 has a slurred elevation
- ✓ Subject 2 has a notched elevation
- ✓ Both subjects died from arrhythmia during the follow-up period

DEMOGRAPHICS

- ✓ J-point elevation of at least 0.1 mV was present in 630 (5.8%) of participants at baseline

- ✓ Those with inferior lead J-point elevation were more often:
  - male, smokers
  - had a lower resting heart rate
  - a lower body mass index, lower blood pressure
  - a shorter QTc interval, a longer QRS duration
  - and were more likely to have ECG evidence of coronary artery disease

- ✓ Those with lateral J-point elevation were:
  - more likely to have left ventricular hypertrophy

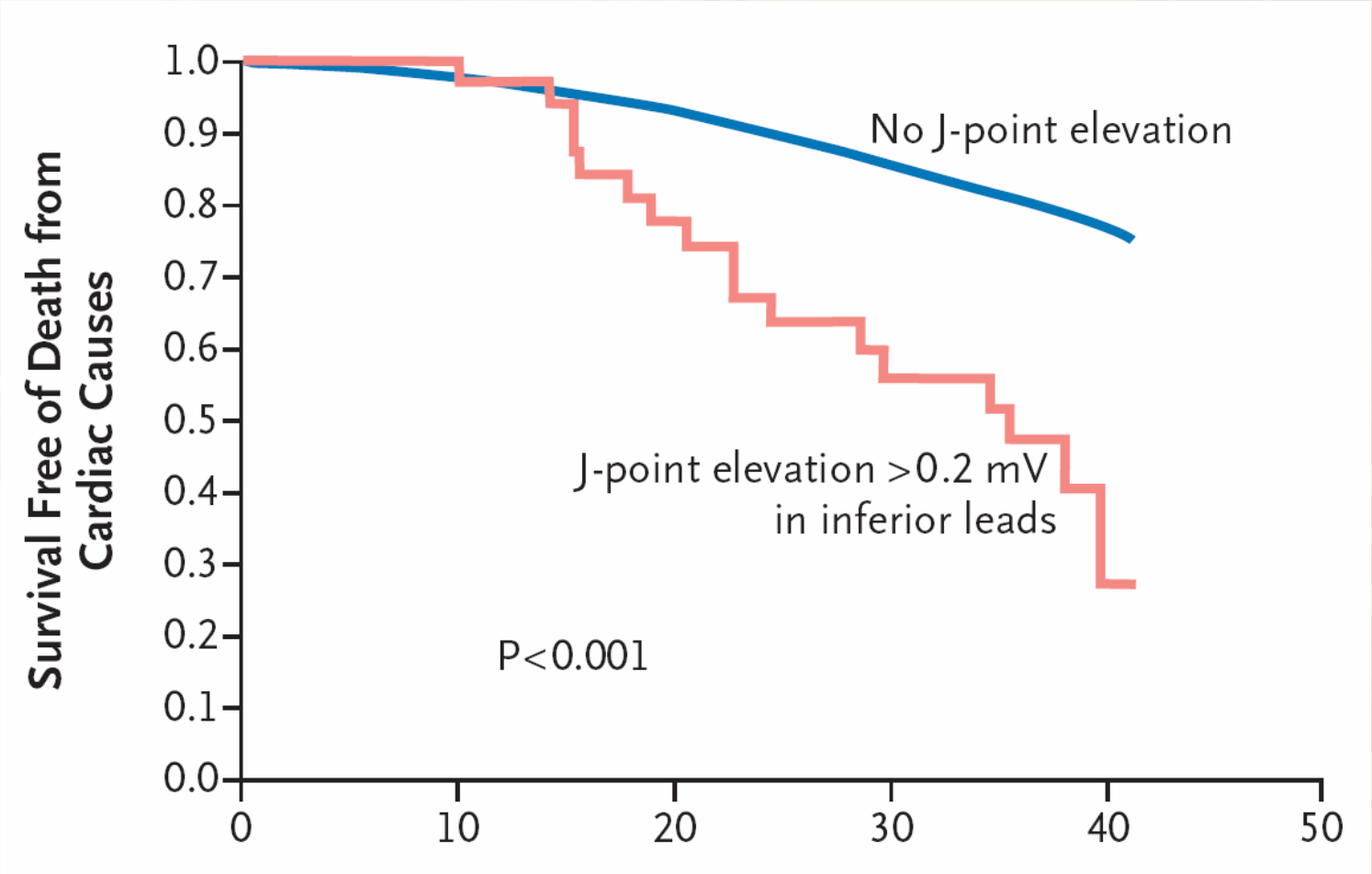
RESULTS

- ✓ During follow-up of 30±11 years, 6133 (56.5%) patients died
- ✓ Of these deaths, 1,969 (32%) were due to cardiac causes, and of those, 795 (40%) were sudden
- ✓ Before and after multivariable adjustment, subjects with J-point elevation of at least 0.1 mV in the inferior leads (n=384) had:
  - a higher risk of cardiac death (adjusted RR= 1.28, p=0.03) and arrhythmic death (adjusted RR= 1.43, p=0.03)
- ✓ However, these patients did not have a significantly higher rate of all-cause mortality

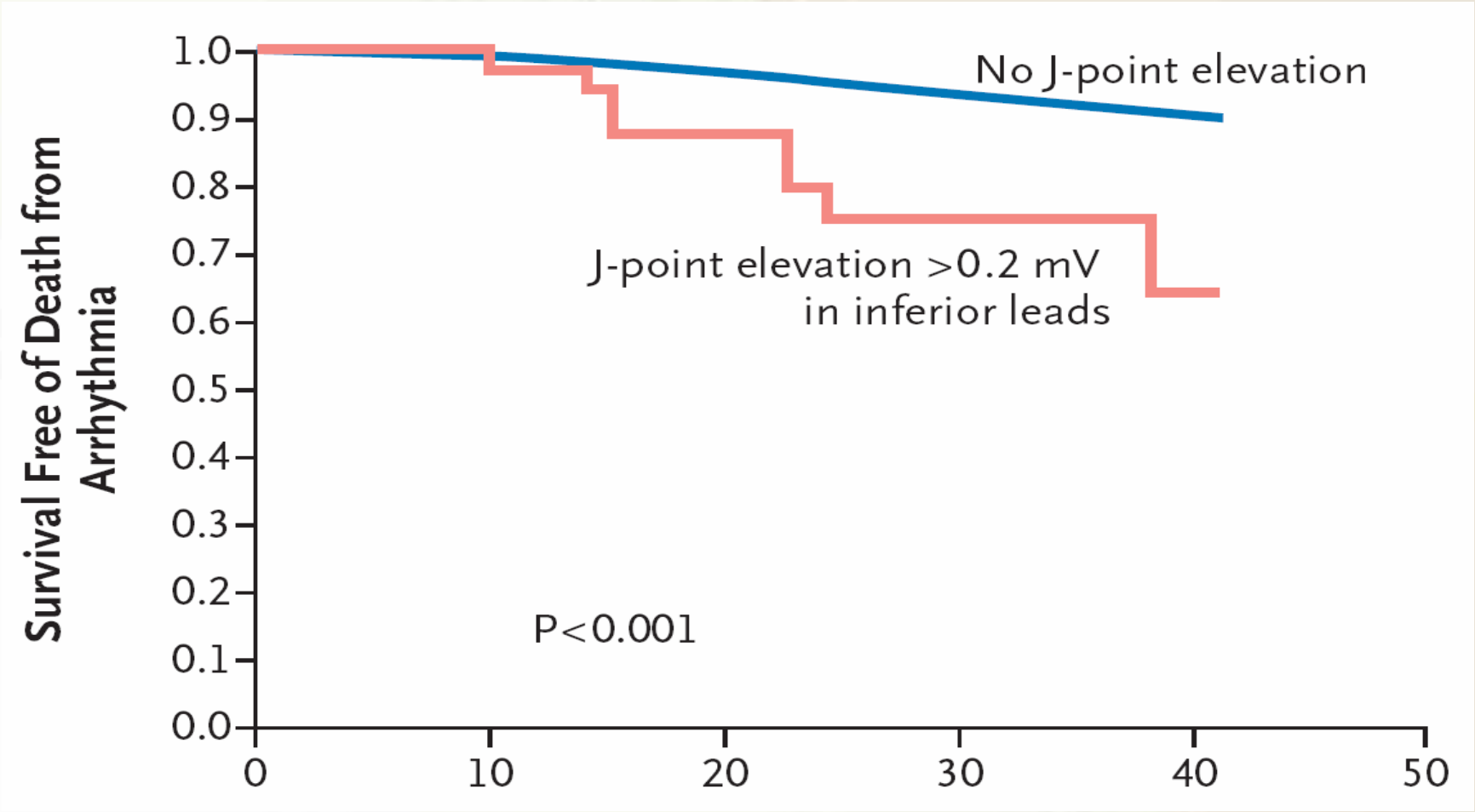
RESULTS

- ✓ Before and after multivariable adjustment, subjects with J-point elevation of 0.2 mV (n=36) had:
  - an increased risk of cardiac death (adjusted RR=2.98, p=0.03)
  - an increased risk of arrhythmic death (adjusted RR=3.94, p=0.03)
  - and death from any cause (adjusted RR= 1.54, p=0.03)
- ✓ Although J-point elevation in the lateral leads was associated with arrhythmic death, it predicted cardiac and all-cause death with borderline significance

Survival Free of Death from Cardiac Causes



Survival Free of Death from Arrhythmia



Comments

- ✓ Early repolarization appears to be associated with worse cardiovascular outcomes, but the exact mechanism remains to be elucidated
- ✓ The mechanism may also differ between patients
- ✓ Although the event rates were relatively high, particularly in those with J-point elevation > 2.0 mV, the follow-up was quite long
- ✓ Additional research is needed to narrow down the particular patients at highest risk and to inform us about screening strategies and ultimately preventive therapies
- ✓ It does appear that inferior lead J-point elevation and particularly prominent J-point elevation may be important risk factors

Systematic Assessment of Patients With Unexplained Cardiac Arrest

CA Survivors With Preserved EF Registry (CASPER) (*Circulation*. 2009;120:278-285)

- ✓ Although an implantable cardioverter-defibrillator (ICD) is an effective tool for secondary prevention in individuals who have suffered a cardiac arrest without a reversible cause, determining the etiology of the event remains important
- ✓ Although coronary artery disease and systolic dysfunction represent the most common precipitants, cardiac arrest survivors without evident cardiac disease remain a challenge to diagnose
- ✓ Determining the cause:
  - can help guide adjuvant therapy
  - can help inform appropriate patient counseling regarding activity and particular drugs to avoid
  - and can help determine whether family screening is beneficial

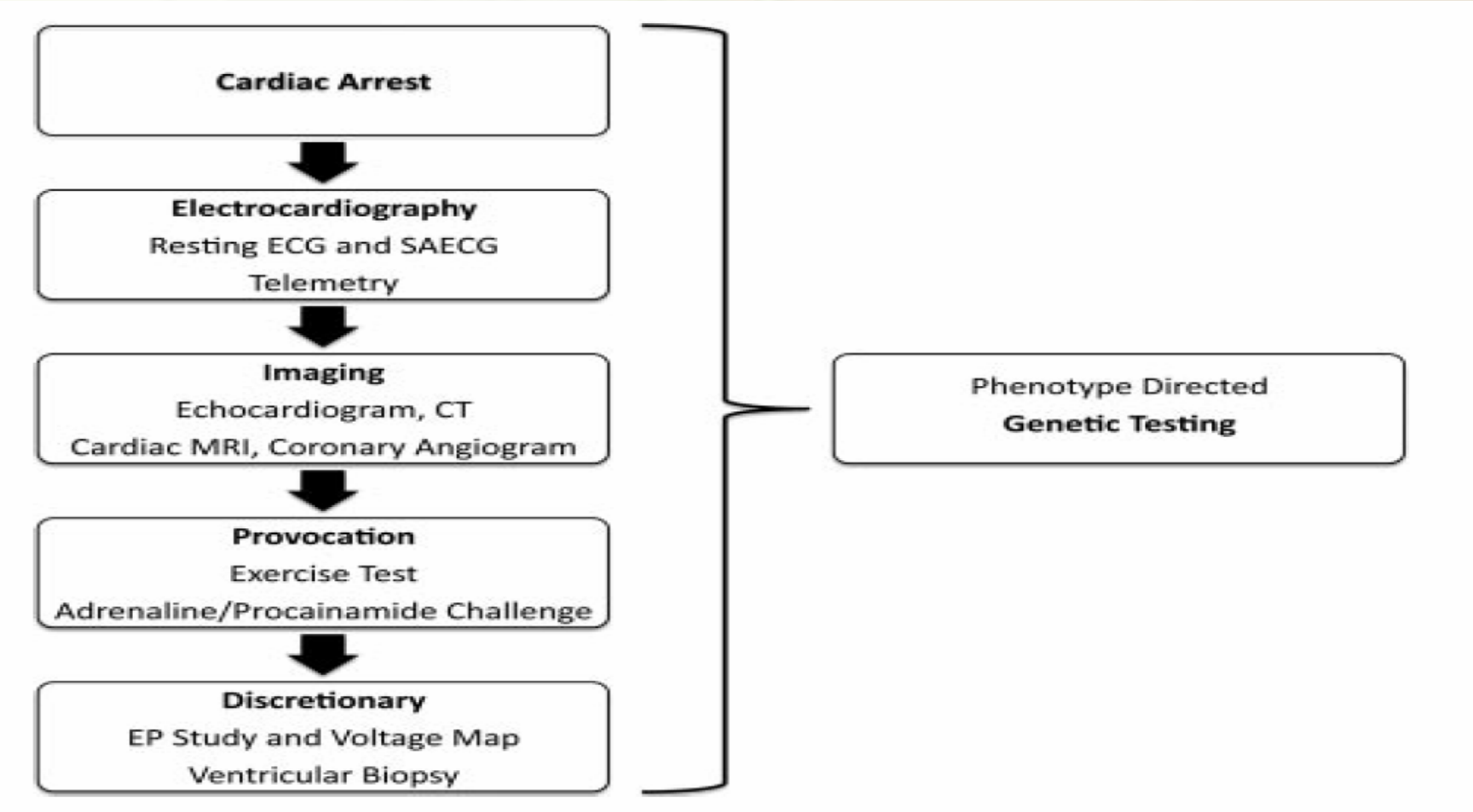
CASPER

- ✓ A prospective study in 9 centers across Canada wherein patients with unexplained cardiac arrest and no evident cardiac disease underwent systematic evaluation including:
  - cardiac magnetic resonance imaging (MRI)
  - signal-averaged ECG
  - exercise testing
  - drug challenge (including IV epinephrine and procainamide)
  - and selective invasive electrophysiological testing and/or endomyocardial biopsy
- ✓ Early repolarization was defined as J-point elevation of at least 0.1 mV in at least 2 inferior or lateral leads
- ✓ Over approximately 4 years, 63 patients with unexplained cardiac arrest were identified
- ✓ All had an ejection fraction 50% and normal coronary arteries

RESULTS

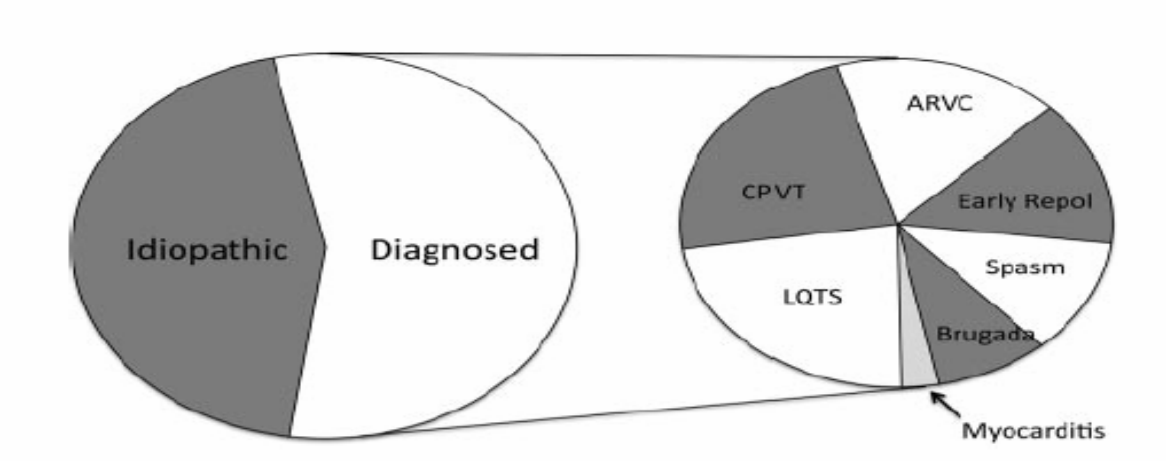
- ✓None had overt evidence of:
  - prolonged QT interval
  - arrhythmogenic right ventricular cardiomyopathy (ARVC)
  - Brugada syndrome
  - ST-segment elevation
  - evidence of hypertrophic cardiomyopathy on imaging
  - anomalous coronary arteries
  - had experienced commotio cordis
  - or had a regular wide complex tachycardia consistent with idiopathic VT

Diagnostic flow diagram



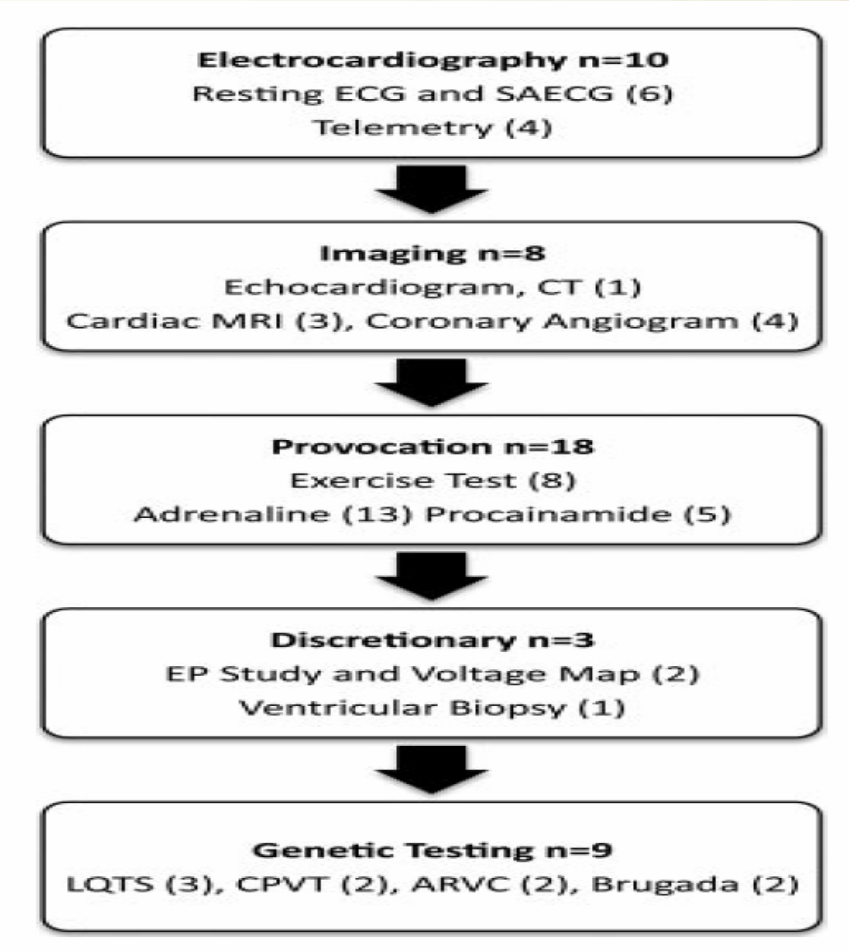
Diagnostic yield

- ✓ Diagnostic yield in 63 patients with unexplained cardiac arrest
- ✓ A diagnosis was obtained in 35 patients (56%), broken down into
  - subclinical primary electrical disease in 24 patients (69%)
  - and structural disease in 11 (31%).



Diagnostic yield

- ✓With the systematic testing:
  - – 35 patients (56%) received a specific diagnosis
    - ✓long QT syndrome (LQTS) was diagnosed in 8 (23%)
    - ✓catecholaminergic polymorphic VT was diagnosed in 8 (23%)
    - ✓ARVC in 6 (17%)
    - ✓early repolarization in 5 (14%)
    - ✓coronary spasm in 4 (11%)
    - ✓Brugada syndrome in 3 (9%)
    - ✓and myocarditis in 1 (3%)



- ✓ Provocative testing had the highest yield of all the different components, with abnormal findings in 18 patients (29%)

Genetics

- ✓ Subsequent targeted genetic testing was performed in 19 patients, and evidence of a causative mutation was found in 9 (47%)
- ✓ Family screening of 64 family members of the 9 patients with causative mutations resulted in the discovery of mutations in 15 (24%), including:
  - 2 with LQTS
  - 4 with Brugada syndrome
  - and 9 with catecholaminergic polymorphic VT
- ✓ This important paper provides a useful algorithm that can serve as a guide in evaluating these patients, potentially helping to guide the most appropriate therapy and focused genetic testing