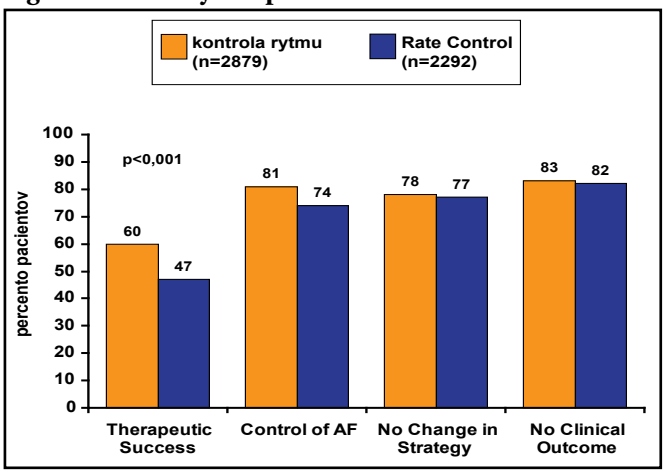
been reported. John Camm, MD, St. George's Hospital Medical School, London, UK, reported results from a real-life, international, observational, prospective, longitudinal cohort study that confirmed and complemented results from these previous controlled randomized trials.

The RecordAF (REgistry on Cardiac rhythm disORDers: an international observational prospective survey assessing the control of Atrial Fibrillation) registry was established to trace the influence of a physician's choice of a rate versus rhythm control strategy on clinical outcome for patients with first onset or recent recurrent AF. Patients (n=5604) aged 18 years and older with a <1-year history of AF were selected from 532 randomly chosen general cardiology practices in 21 countries. Patients with permanent or transient AF were not eligible. The primary study endpoint was the rate of therapeutic success of AF management (in sinus rhythm or at rate control target with no major CV event and no change in strategy) at 12 months. The co-primary endpoint was the rate of major CV events (eg, CV death, myocardial infarction, stroke, transient ischemic attack [TIA], and hospitalizations).

At baseline, 45.1% (n=2528) of patients in the registry were being treated with a rate control strategy and 54.9% (n=3076) were treated with a rhythm control strategy. Patients in the rhythm control group were an average of 3 years younger than those on rate control (64 vs 67 years; p<0.001) and had a significantly (p<0.001) lower resting heart rate (76.6 vs 80.6 beats per minute). Body mass index and systolic blood pressure were slightly but significantly (p=0.008 and p=0.02, respectively) greater in the rhythm control group.

Data for 92.3% of patients were available after 1 year of follow-up, at which time more patients in the rhythm control group were in sinus rhythm (81% vs 33%). Approximately 50% of patients had a change in pharmacological treatment and 20% had a change in therapeutic strategy in both groups. Therapeutic success was achieved significantly (p<0.001) more frequently in patients who were treated by rhythm control (60% vs 47%), which was driven by control of AF (Figure 1). For the co-primary endpoint, there was no difference (p=0.35) between the two strategies in terms of overall clinical events (18% in rate control vs 17% in rhythm control groups). Multivariate analysis showed that the occurrence of cardiovascular clinical events was more dependent on comorbidity (coronary artery disease, heart failure, age >75 years, renal disease, prior stroke/TIA) than the choice of strategy. Hospitalizations for arrhythmia were more common in the rhythm (11%) versus rate control group (7%), and hospitalizations for heart failure management were more common in the rate (5%) versus rhythm control group (2%).

Figure 1. Primary Endpoint at One Year.



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Prof. Camm concluded that although successful management of AF was achieved more often with rhythm control, this did not translate into better outcomes.

New Data from RE-DEEM and RE-LY

Results from the Phase II dose-ranging RE-DEEM trial (NCT00621855), presented by Jonas Oldgren, MD, Uppsala Clinical Research Center, Uppsala, Sweden, indicate that dabigatran up to 150 mg BID can be used in conjunction with dual antiplatelet therapy with only modestly increased bleeding risk.

RE-DEEM compared four dose regimens of dabigatran versus placebo in patients on dual antiplatelet therapy after acute coronary syndrome (ACS). The primary study endpoint was major (ISTH criteria) and clinically relevant minor bleeding. Secondary endpoints included coagulation activity and a composite of cardiovascular (CV) death, nonfatal myocardial infarction (MI), and nonhemorrhagic stroke.

Subjects (n=1878; mean age 61.8 years; 76% men) with ST or non-ST elevation ACS and ≥1 additional risk factor for CV complications who were already on dual antiplatelet therapy were randomly assigned to receive placebo or dabigatran 50 mg, 75 mg, 110 mg, or 150 mg BID for 6 months. The most common risk factors for CV complications were age ≥65 years (44%), diabetes (31%), previous MI (29%), and no revascularization for the index event (31%).

There was a significant dose-dependent (p<0.001) increase in the primary endpoint of major or clinically relevant minor bleeding (Figure 1). A comparison of major bleeding using the 3 major definitions showed a <1% increase with the highest dabigatran dose or with the two top doses combined (Table 1).

Figure 1. Primary Outcome: Bleeding.

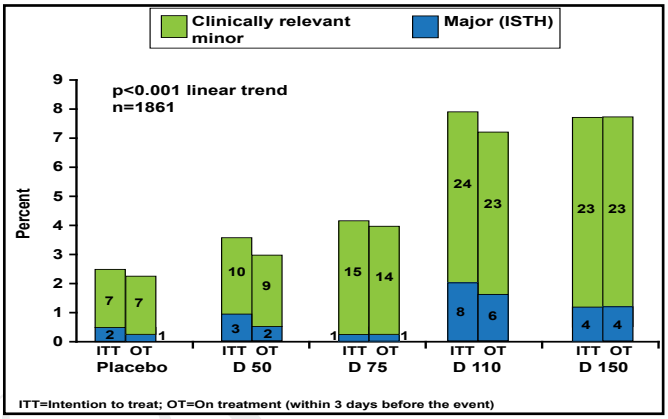

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Table 1. Major Bleeding Comparison.

	Placebo	Dabigatran			
	n=371	50 mg BID n=369	75 mg BID n=368	110 mg BID n=406	150 mg BID n=347
ISTH Major*	0.5%	0.8%	0.3%	2.0%	1.2%
TIMI Major	0.3%	0.3%	0	1.2%	0.3%
GUSTO Severe	0.3%	0.3%	0	0.5%	0

* Part of the primary composite outcome

Treatment with dabigatran doses resulted in a 45% reduction in D-dimer levels compared with placebo. There was a low rate of events for the composite secondary endpoint of CV death, nonfatal MI, and stroke. The study was not powered to show a difference between groups.

Dabigatran was well tolerated. Serious adverse events (AEs) were similar between the dabigatran doses and placebo, although slightly more dabigatran patients discontinued treatment, mostly due to bleeding. There was one fatal bleed in the placebo group and one in the 110 mg dabigatran group. There were no intracranial or intraspinal bleeds in any of the dose arms.

The investigators concluded that these results support the rationale for evaluating the 110- and 150-mg doses of dabigatran on clinical outcome in ACS in a larger study.

Lars Wallentin, MD, Uppsala Clinical Research Center, Uppsala, Sweden, presented the results of a post hoc analysis of data from the RE-LY trial (NCT00262600), showing that the reduction in the incidence of stroke and major bleeding in patients with atrial fibrillation (AF) that was seen in RE-LY was independent of the quality of INR control that was achieved at the individual study centers. For secondary outcomes, such as all vascular events and mortality, the advantage of dabigatran may be greater at centers with poorer INR control.

RE-LY was a prospective noninferiority trial that evaluated the safety and efficacy of dabigatran versus warfarin for stroke prevention in AF. Subjects were randomly assigned to open-label treatment with warfarin (INR 2.0 to 3.0; n=6022) or blinded treatment with dabigatran 110 mg BID (n=6076) or 150 mg BID (n=6015). Dabigatran 110 mg BID was shown to be noninferior to warfarin, and dabigatran 150 mg BID was superior to warfarin in reducing the incidence of stroke and systemic embolism (RR, 0.66; 95% CI, 0.53 to 0.82; p<0.001). There was no significant difference in the rate of major bleeding for dabigatran 150 mg BID versus warfarin (3.11% and 3.36% per year, respectively; p=0.31); the rate of major bleeding with dabigatran 110 mg BID (2.71% per year) was 20% lower versus warfarin (p=0.003) [Connolly SJ et al. *N Engl J Med* 2009].

This post hoc analysis was conducted to determine whether the dabigatran results were influenced by variations in the quality of INR control at the individual centers. The center average time in treatment range (TTR) in the warfarin arm was applied as a proxy for all patients at all centers and used to stratify patients into quartiles (<56.9%, 56.9% to 65.4%, 65.5% to 72.4%, and >72.4%). The primary endpoint was stroke or systemic embolism.

Results from the analysis were consistent with those from the overall study for the primary outcome and for the secondary outcomes of reduced intracranial and major bleeding, regardless of center TTR level. Indications of an interaction with center TTR level was seen for mortality, with dabigatran reducing mortality at centers with poor INR control but not those with good INR control. In the overall trial results, there was a significant reduction in all CV events (vascular events, death, and major bleeding) with dabigatran. In this analysis, these reductions appeared to be most relevant to those centers with poor INR control (Table 2).

Although acknowledging the limitations of the analysis, Prof. Wallentin concluded that these results appear to confirm the overall results of the RE-LY trial and provide additional information on how levels of INR control may influence outcomes.

Table 2. Event Reductions.

Center TTR Quartiles Range	D 110 mg BID vs warfarin RR (95% CI)	p value for Interaction	D 150 mg BID vs warfarin RR (95% CI)	p value for Interaction
Primary Endpoint of Stroke or Systemic Embolism				
<56.9%	1.1 (0.73, 1.6)		0.61 (0.39, 0.96)	
56.9% - 65.4%	0.74 (0.51, 1.1)		0.48 (0.32, 0.74)	
65.5% - 72.4%	1.0 (0.65, 1.5)		0.76 (0.48, 1.21)	
>72.4%	0.88 (0.57, 1.4)		0.88 (0.57, 1.37)	
		0.27		0.41
Intracranial Bleeding				
<56.9%	0.56 (0.23, 1.3)		0.62 (0.27, 1.4)	
56.9% - 65.4%	0.25 (0.12, 0.55)		0.38 (0.19, 0.74)	
65.5% - 72.4%	0.22 (0.07, 0.65)		0.44 (0.19, 1.0)	
>72.4%	0.31 (0.13, 0.73		0.30 (0.13, 0.71)	
		0.51		0.68
Major Bleeding				
<56.9%	0.66 (0.48, 0.91)		0.74 (0.54, 1.0)	
56.9% - 65.4%	0.79 (0.60, 1.0)		0.84 (0.41, 1.1)	
65.5% - 72.4%	0.90 (0.67, 1.2)		1.12 (0.85, 1.5)	
>72.4%	0.84 (0.62, 1.1)		1.08 (0.81, 1.4)	
		0.22	0.10	0.10
Total Death				
<56.9%	0.71 (0.56, 0.90)		0.68 (0.54, 0.86)	
56.9% - 65.4%	0.96 (0.75, 1.24)		0.91 (0.70, 1.2)	
65.4% - 72.4%	0.92 (0.70, 1.21)		1.0 (0.78, 1.3)	
>72.4%	1.1 (0.87, 1.5)		1.0 (0.78, 1.4)	
		0.02		0.02
All Cardiovascular Events*				
<56.9%	0.75 (0.62, 0.89)		0.69 (0.57, 0.82)	
56.9% - 65.4%	0.93 (0.78, 1.1)		0.88 (0.73, 1.1)	
65.5% - 72.4%	1.1 (0.87, 1.3)		1.1 (0.92, 1.4)	
>72.4%	1.0 (0.83, 1.2)		1.0 (0.85, 1.3)	
		0.04		0.002

* Vascular events, death, major bleeding; D = dabigatran.

Biventricular Pacing Protects Against Adverse Cardiac Remodeling Associated with Right Ventricular Pacing

Pacing both ventricles of the heart, rather than pacing the right ventricle only, prevented loss of left ventricular function among patients with sinus node dysfunction or bradycardia due to atrioventricular (AV) block, according to new findings from the Pacing to Avoid Cardiac Enlargement (PACE) trial (CUHK_CCT00037).

Right ventricular apical (RVA) pacing is associated with deleterious effects on left ventricular systolic function and adverse clinical outcomes, including progression to heart failure, in patients with standard pacing indications. By comparison, biventricular (BiV) pacing has been shown to slow or reverse progressive adverse ventricular remodeling in certain patients, such as those with heart failure. The PACE trial was designed to evaluate whether BiV pacing is superior to RVA pacing in preserving left ventricular systolic function and avoiding adverse left ventricular structural remodeling in patients with normal left ventricular ejection fraction (LVEF).

Cheuk-Man Yu, MD, Chinese University of Hong Kong, Hong Kong, China, presented results from the PACE trial, which were simultaneously published online in *The New England Journal of Medicine*.

The PACE trial included 177 patients with a normal LVEF (>45%) who had sinus node dysfunction or AV block. Patients were randomly assigned to BiV (n=89) or RVA (n=88) dual-chamber pacing. The primary endpoints were LVEF and left ventricular end-systolic volume (LVESV) at 12 months.

Baseline characteristics were similar in both treatment groups. In the BiV pacing group, the mean age was 69 years, LVEF was 61.9%, and the indication for pacing was advanced AV block in 55% of patients and sinus node dysfunction in 45% of patients.

During the first year, LVEF fell in the RVA group but remained unchanged in the BiV group, leading to an absolute difference of 7.4% between groups at 12 months (p<0.001; Figure 1). Fewer patients in the BiV group than in the RVA group experienced a decline in LVEF to <45% (1% vs 9%; p=0.02). At 12 months, LVESV was significantly lower in the BiV group than in the RVA group (27.6 ml vs 35.7 ml; p<0.001), reflecting a relative change from baseline that was 25% greater in the RVA group than in the BiV group (p<0.001).