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Effect of ranolazine on atrial fibrillation in patients with non-ST elevation acute coronary syndromes: observations from the MERLIN-TIMI 36 trial

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Aims To determine the effect of ranolazine, an anti-ischaemic agent with anti-arrhythmic properties, on the overall burden of atrial fibrillation (AF) in acute coronary syndromes (ACS) and determine whether ranolazine reduces the long-term incidence of clinical AF after ACS.

Methods and results MERLIN-TIMI 36 randomized patients with non-ST elevation ACS to ranolazine or placebo. Atrial fibrillation episodes detected on continuous electrocardiogram (cECG) monitoring were reviewed in 6351 patients (97% of trial). Atrial fibrillation burden was categorized according to the time in AF: clinically insignificant AF (<0.01% of time), paroxysmal AF (>0.01–98%), or predominantly persistent AF (>98%). Clinical AF events were identified through adverse event reporting for a median 1-year follow-up. Overall, patients assigned to ranolazine had a trend towards fewer episodes of AF [75 (2.4%) vs. 55 (1.7%) patients, $P = 0.08$] detected on cECG during the first 7 days after randomization. The pattern of new-onset AF differed between ranolazine vs. placebo: clinically insignificant AF (five patients in ranolazine vs. seven in placebo), paroxysmal AF (18 vs. 48 patients), and predominantly chronic AF (28 vs. 20 patients, three-way $P < 0.01$). Among patients with a paroxysmal AF pattern, the overall burden was lower with ranolazine than with placebo (median 4.4 vs.16.1%, $P = 0.015$). Over the median 1-year follow-up, fewer patients treated with ranolazine experienced an AF event compared with placebo (2.9 vs. 4.1%, RR 0.71, $P = 0.01$).

Conclusion Ranolazine, an anti-anginal agent with electrophysiological effects, may reduce the frequency of paroxysmal AF in patients with non-ST elevation ACS with a pattern of lower overall AF burden in this group. Ranolazine reduced the overall 1-year incidence of clinical AF events. These atrial-specific anti-arrhythmic properties of ranolazine may be of clinical interest and warrant additional investigation.

Clinical trial registration NCT00099788.

Keywords Atrial fibrillation • Ranolazine • Anti-arrhythmic therapy • Acute coronary syndromes

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias encountered in clinical practice. Although acute ischaemia is likely a less common trigger of AF when compared with other potential aetiologies, AF occurs in 5–10% of patients with acute coronary syndromes (ACS), likely because ischaemia can lead to atrial volume and pressure overload, atrial infarction, or pericarditis.[1–4] The presence of AF during ACS appears to be independently associated with increased short- and long-term mortality.[3,4] However, it is not

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What's new?

- Ranolazine reduced the frequency of paroxysmal atrial fibrillation in patients with acute coronary syndrome (ACS).
- Ranolazine reduced the overall 1-year incidence of clinical AF events after ACS.
- These hypothesis-generating data justify ongoing prospective trials of ranolazine as an atrial anti-arrhythmic agent.

clear from previous studies what proportion of patients had pre-existing AF.

Ranolazine, an inhibitor of the late phase of the sodium current (I_{Na}), is approved for the treatment of chronic stable angina.[5,6] In addition, several studies have identified anti-arrhythmic properties, particularly for ventricular arrhythmias.[7] Because ranolazine also blocks peak I_{Na} in atrial cells, it will, like other agents that block peak I_{Na} (e.g. amiodarone or vernakalant), increase post-repolarization refractoriness, and potentially suppress AF.[8,9] In the MERLIN-TIMI 36 trial, ranolazine reduced the overall incidence of both supraventricular and ventricular tachycardias in patients admitted with Non-ST elevation ACS (NSTEACS), with a trend towards a lower incidence of new-onset AF on continuous electrocardiogram (cECG) monitoring during the first 7 days after randomization.[10,11] However, we have not previously explored the effect of ranolazine on the pattern and overall burden of AF during cECG monitoring and the incidence of clinical events related to AF during longer term follow-up after a hospitalization for NSTEACS.

Methods

In MERLIN-TIMI 36, a total of 6560 patients hospitalized with NSTEACS were randomized to receive either a 200 mg bolus of intravenous ranolazine, with subsequent 80 mg/h infusion for 12–96 h, followed by 1000 mg oral ranolazine twice daily or matching placebo in addition to standard medical and interventional therapy.[12,13] Eligible patients had at least 10 min of ischaemic symptoms at rest and at least one of the following moderate- to high-risk features: elevated biomarkers of myocardial necrosis, ST segment depression $\geq$0.1 mV, history of diabetes mellitus, or an intermediate to high TIMI risk score ($\geq$3). Exclusion criteria include left bundle branch block, predominant ventricular paced rhythm, significant left ventricular hypertrophy, and concurrent digoxin use. Medications that prolonged the QT interval such as Class IA or III anti-arrhythmic agents were prohibited. A cECG recording (Lifecard CF, DelMar Reynolds/Spacelabs) was carried out for the first 7 days after randomization in 6351 patients (97%) to assess for ischaemia and arrhythmias as part of an efficacy and safety analysis.[10,12] As reported previously, baseline characteristics were well balanced between treatment arms.[10,11] The median time from symptom onset to randomization was 24 h. Median clinical follow-up was 12 months. The primary efficacy endpoint of the study was a composite of cardiovascular death, myocardial infarction (MI), or recurrent ischaemia through the end of the study. Analysts and cardiologists blinded to treatment assignment and outcomes determined the presence of ischaemia and arrhythmia in the TIMI ECG Core Laboratory.

In a retrospective assessment, all cases of new-onset AF detected on cECG ($n = 130$) were analysed to assess AF burden (five recordings could not be analysed due to technical reasons). Atrial fibrillation burden was calculated as the proportion of recording time (%) in AF. We found that calculating post-ACS AF burden posed a distinct challenge, as there appeared to be three clinical categories of AF burden. We therefore further categorized patients with AF as those with clinically insignificant AF (<0.01% of the time in AF), paroxysmal AF (>0.01–98%), and predominantly chronic AF (>98%). Clinical AF events over the entire duration of follow-up were identified through adverse event reporting. Events deemed to be serious by the investigator were further adjudicated by a blinded CEC to determine if the event was symptomatic and related to AF. The mean clinical follow-up was 348 days.

Statistical analysis

Continuous data were compared with a *t* test for normally distributed data and a Wilcoxon rank-sum test for non-normally distributed data. Dichotomous variables were compared using a χ^2 test. All analyses comparing the treatment strategy and the incidence of arrhythmias were performed with the Cochran–Mantel–Haenszel test stratifying by the intention to use an early invasive strategy, consistent with the main analysis plan. Time to new onset of AF was analysed based on a Cox proportional-hazards regression model, and hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. Mortality rates are presented as Kaplan–Meier failure rates at 12 months. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline characteristics of patients with cECG recordings are summarized in *Table 1*. Age, cardiovascular history were well balanced between treatment groups, as were utilization of beta-blockers, angiotensin-converting enzymes/angiotensin receptor blockers, and statin use during index hospitalization and at discharge.

Patients with new-onset AF were older and more likely to have a history of heart failure, present with NSTEMI than unstable angina, have reduced left ventricular function and impaired renal function compared with patients without AF. (*Table 2*) The 1-year incidence of death from cardiovascular causes as well as any cause was higher in patients with new-onset AF compared with patients without new-onset AF (10.4 vs. 4.3% for CV death and 12.1 vs. 5.0% for all-cause death). These associations were attenuated after adjusting for TIMI risk score, history of heart failure, and renal function (HR_{adj} 1.49, 95% CI 0.85–2.61, $P = 0.16$ for CV death and HR_{adj} 1.50, 95% CI 0.89–2.52, $P = 0.13$ for overall mortality).

Overall, patients assigned to ranolazine had a trend towards fewer episodes of AF [75 (2.4%) vs. 55 (1.7%) patients, $P = 0.08$] detected on cECG during the first 7 days after randomization. The pattern of AF burden on cECG was significantly different among patients assigned to ranolazine vs. placebo [paroxysmal AF (>0.01–98%, 18 patients on ranolazine vs. 48 on placebo); predominantly chronic AF (28 vs. 20 patients); and clinically insignificant AF (5 vs. 7 patients; three-way $P < 0.01$)] (*Figure 1*). Among patients with a paroxysmal AF pattern, the overall burden was lower in patients assigned to ranolazine compared with placebo (median 4.4 vs.16.1%, $P = 0.015$, *Figure 2*).

Over the median 1-year clinical follow-up, fewer patients assigned to ranolazine reported any clinical AF event compared with placebo (2.9 vs. 4.1%, HR 0.71, 95% CI 0.55–0.92, $P = 0.01$, *Figure 3*), though there was no difference in the incidence of AF events that were

Table 1 Baseline characteristics in patients with continuous ECG monitoring

Characteristics	Ranolazine ($n = 3162$)	Placebo ($n = 3189$)
Age ≥75 years	17.0	18.0
Female (%)	33.8	36.3
Comorbidities (%)		
Diabetes	33.6	34.1
Hypertension	73.4	74.0
Current smoker (%)	26.5	24.3
Cardiac history (%)		
Prior MI	34.4	34.0
Prior heart failure	16.5	17.2
Creatinine clearance <60 mL/min (%)	21.4	21.6
Index event (%)		
Unstable angina	47.1	46.6
Non-ST-elevation MI	51.0	50.9
Other	1.9	2.5
TIMI risk score (%)		
0–2	26.9	26.7
3–4	52.4	52.8
5–7	20.7	20.5
LVEF <40% (if known) (%)	13.9	13.4
Cardiac medications during index hospitalization (%)		
Aspirin	96.2	96.0
Beta-blocker	88.8	89.7
ACE inhibitor or ARB	77.5	78.9
Statin	82.6	81.9

No significant differences between treatment groups, except gender ($p = 0.03$).

Table 2 Baseline characteristics in patients with and without new-onset AF detected on continuous ECG monitoring

Characteristics	New-onset AF ($n = 130$)	No new-onset AF ($n = 6211$)	*P* value
Age ≥75 years (%)	41.5	17.0	<0.001
Female (%)	36.9	35.0	0.65
Comorbidities (%)			
Diabetes	36.2	33.9	0.58
Hypertension	76.6	73.6	0.45
Current smoker (%)	13.1	25.7	0.001
Cardiac history (%)			
Prior MI	31.0	34.2	0.45
Prior heart failure	25.4	16.7	0.008
Creatinine clearance <60 mL/min (%)	36.9	21.1	<0.001
Index event (%)			<0.001
Unstable angina	30.0	47.1	
Non-ST-elevation MI	69.2	50.6	
Other	0.8	2.3	
TIMI risk score (%)			0.034
0–2	16.9	27.1	
3–4	60.8	52.4	
5–7	22.3	20.5	
LVEF <40% (if known) (%)	25.0	13.4	0.001
Cardiac medications during index hospitalization (%)			
Aspirin	92.3	96.2	0.02
Beta-blocker	91.5	89.2	0.39
ACE inhibitor or ARB	85.4	78.0	0.045
Statin	83.8	82.2	0.63

adjudicated to be both symptomatic and related to AF (0.10 vs. 0.12%, HR 0.81, 95% CI 0.51–1.32 $P = 0.41$).

Discussion

In over 6300 patients admitted with NSTEACS, documented episodes of new AF occurred infrequently during the first days after hospitalization and occurred more often in older patients with greater comorbidity and high-risk features of their ACS presentations. Ranolazine, an anti-anginal agent with electrophysiological effects, reduced the frequency of patients with a paroxysmal pattern of AF, and reduced overall AF burden in this group. During 1-year follow-up, ranolazine reduced the overall incidence of AEs related to AF. These findings provide intriguing additional evidence suggesting possible clinically relevant electrophysiological effects of ranolazine, now with regard to AF.

The proposed anti-arrhythmic effects of ranolazine are relatively well described for ventricular arrhythmias. Inhibition of late I_{Na} reduces both the substrates and triggers ventricular ectopy such as increased spatial and temporal dispersion of repolarization and early after-depolarizations.[7,14,15] Ranolazine significantly reduced the incidence of non-sustained VT in the MERLIN-TIMI 36 trial[11]

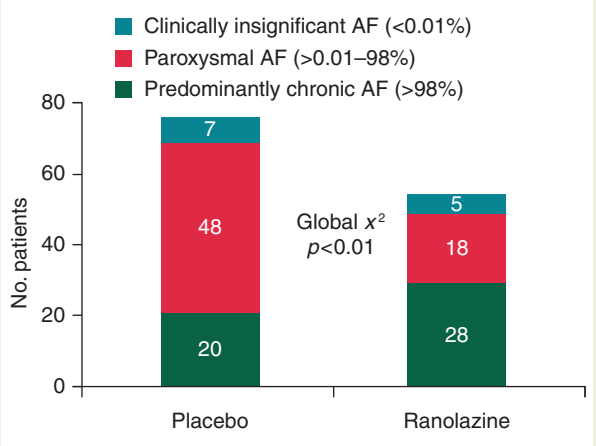

Figure 1 Distribution of the pattern of AF detected on cECG during the first 7 days post admission.

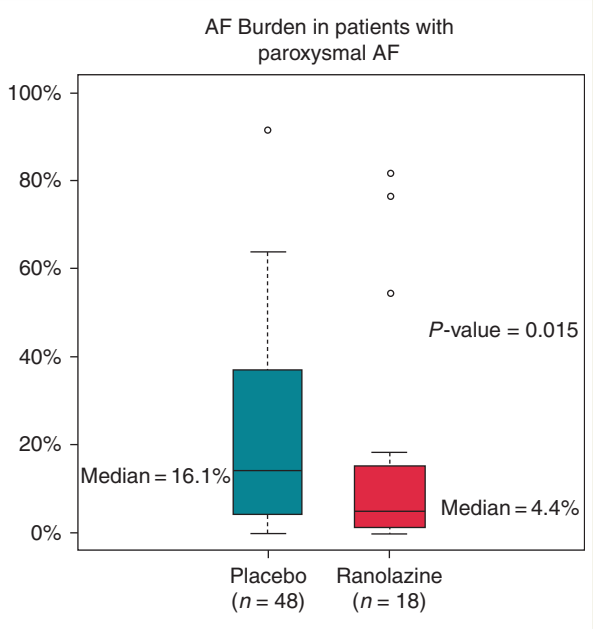

Figure 2 Comparisons between placebo and ranolazine of the percentage of AF burden in patients with a paroxysmal pattern of AF. The median was 14.1% (interquartile range 4.1 and 35.1%) for placebo and 5.1% (interquartile range 1.1 and 15.1% for ranolazine).

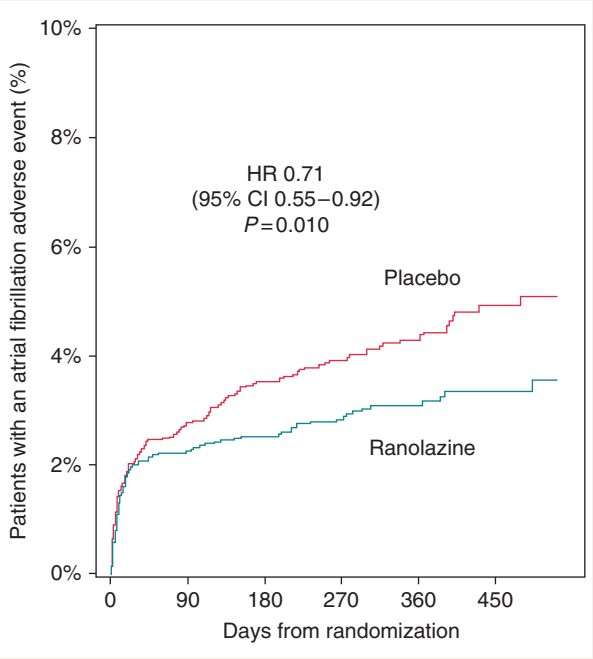

Figure 3 Clinical AF events in patients treated with ranolazine or placebo during entire 1-year follow-up.

and is currently under evaluation in the ranolazine implantable cardioverter-defibrillator study of over 1400 patients with ischaemic or nonischaemic cardiomyopathy and implantable defibrillators (ICDs) to determine if it will reduce the risk of ventricular tachycardia or ventricular fibrillation requiring anti-tachycardic pacing therapy, ICD shock, or death.[16]

Potential atrial effects of ranolazine

There are several proposed mechanisms by which ranolazine may reduce atrial susceptibility to fibrillation. Initiation of AF is often triggered by a focal activation such as early or late after-depolarizations, which can be precipitated by intracellular calcium overload.[7,17] Inhibition of late I_{Na} with ranolazine reduces intracellular sodium concentrations and the subsequent calcium overload, thus reducing the triggered activity that promotes AF. In contrast to the electrophysiological actions of ranolazine in the ventricle, where inhibition of the late I_{Na} is believed to be the primary basis for its anti-arrhythmic effect, the predominant mechanism of action in the atria is via inhibition of peak I_{Na}. Unlike prototypical Class I sodium channel blockers, the effect of ranolazine on peak I_{Na} is atrial selective and has distinct kinetics.[6] This atrial selective inhibition of peak I_{Na} by ranolazine decreases the atrial action potential upstroke, increases diastolic threshold of excitation and post-repolarization refractoriness.[8,9,17] Ranolazine may further reduce the atrial susceptibility to fibrillation through inhibition of I_{Kr} and late I_{Na} in the atria. The anti-ischaemic effect of ranolazine is therefore not likely the sole reason for its potential anti-arrhythmic effects; however, a contribution cannot be ruled out.[18] The apparent benefit of ranolazine in patients with paroxysmal AF, as opposed to persistent AF, likely reflects the proposed anti-arrhythmic mechanism of ranolazine, which is to decrease the triggered activity that initiates AF. It may be less effective converting AF to normal sinus rhythm.

During large animal studies, ranolazine significantly reduced AF frequency with a trend towards suppression of AF re-initiation after administration of acetylcholine into the pericardial space.[19] In this model, ranolazine also lowered the dominant frequency of AF, which suggests that it may increase atrial electrical organization and thereby improve the odds of successful cardioversion. Several small, single-centre studies in humans have reported that ranolazine reduces the risk of AF after cardiac surgery compared with amiodarone[20] and improves the chance of conversion to sinus rhythm when used together with amiodarone[21,22] or in cardioversion-resistant patients.[23] Moreover, the HARMONY Study (A study to evaluate the effect of ranolazine and dronedarone when given alone and in combination in patients with paroxysmal atrial fibrillation), a randomized Phase II trial in patients with paroxysmal AF found that the combination of ranolazine and dronedarone (but not either alone) significantly reduced the risk of AF compared with placebo.[24]

Overall, the incidence of new-onset AF was lower in this cohort than previously reported in other studies of ACS.[2–4] This finding may be explained in part due to differences in patient characteristics and in the methods for classification of new-onset AF. In this study, AF was limited to cases where it was determined to be *new-onset* AF as detected in cECG, which was not utilized in other prior studies.[2] Moreover, MERLIN-TIMI 36 did not include patients presenting with STEMI or those taking digoxin and Class IA or III anti-arrhythmic agents, further reducing the number of patients at highest risk for arrhythmias.

In contrast to other clinical trials or community-based studies of patients with ACS, the utilization of cECG permitted the evaluation

of the overall pattern and burden of AF, demonstrating a reduced overall burden with ranolazine in patients with a paroxysmal pattern of AF. In patients who were predominantly in AF, ranolazine did not lead to any difference in AF burden, suggesting that ranolazine alone may not be sufficient to promote chemical cardioversion in patients with more persistent AF.

This analysis has several limitations. This was a *post-hoc* analysis, prompted by pre-clinical studies of ranolazine suggesting selective atrial anti-arrhythmic activity.[8,9] Due to the post-NSTEACS population, these observations cannot be generalized to include all types of AF nor to other populations. Ascertainment of AF events did not include comprehensive regular telemetry monitoring, which likely would have detected more episodes of AF, but was limited to symptomatic events that achieved AE reporting criteria. Because of the low event rate, we cannot exclude the possibility of a Type I error. The method of AF burden categorization was performed *post-hoc* and therefore requires future validation. Moreover, because ranolazine exerts anti-ischaemic effects via inhibition of the late phase of I_{Na}, which by itself could raise the AF threshold, we cannot determine if suppression of AF could be due to less ischaemia. However, we have observed that other electrophysiological effects of ranolazine were not mediated by reductions in ischaemia alone.[11]

Conclusion

In summary, in the setting of ACS, we found that ranolazine tended to reduce the overall burden of AF and reduced longer-term clinical AF events in the year following ACS. These findings provide interesting support from a randomized placebo-controlled investigation that the potential atrial-specific anti-arrhythmic properties of ranolazine may be of clinical interest and warrant additional investigation. Demonstrating clinical effectiveness in suppressing AF will require additional studies. Ongoing trials of ranolazine[25–27] either alone will further elucidate the potential role of ranolazine in the treatment of a broader population of patients with paroxysmal or persistent AF.

Conflicts of interest: B.M.S. reports research grants via the TIMI Study and Brigham and Women's Hospital from AstraZeneca and Bristol-Myers Squibb, Daichi-Sankyo, GlaxoSmithKline, Johnson and Johnson, Bayer Healthcare, Gilead, Eisai, Merck. Consulting fees from Gilead, Lexicon, Arena, Eisai, St. Jude's Medical, Forest Pharmaceuticals, Bristol-Myers Squibb, Boston Clinical Research Institute, Decision Resources, University of Calgary, Elsevier Practice Update Cardiology. L.B., E.K.-P., and M.L.C. are employees of Gilead Science, Inc. B.R.C. reports receiving consultant fees and speaker's bureau from Gilead Consultant fees from Pfizer, Merck, Sanofi, NovoNordisk, Johnson and Johnson, Forest, and Lilly (CEC or DSMB). Research Grants: NIH. E.B. received research grant support (to his institution) from CV Therapeutics (now Gilead) to support the MERLIN-TIMI 36 trial. He also received honoraria and support for travel for his participation in symposia sponsored by CV Therapeutics (now Gilead). D.A.M. is an investigator and receives salary from the TIMI Study Group. He has received remuneration for consulting from Abbott Laboratories, Gilead, Instrumentation Laboratory, Konica Minolta, Johnson & Johnson, Merck, Roche Diagnostics, and Servier. S.A.M. is employed by the TIMI Study Group. J.W. and S.V. have no conflicts to report.

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Superior vena cava syndrome after radiofrequency sinus node modification treated with thrombolysis and stent implantation

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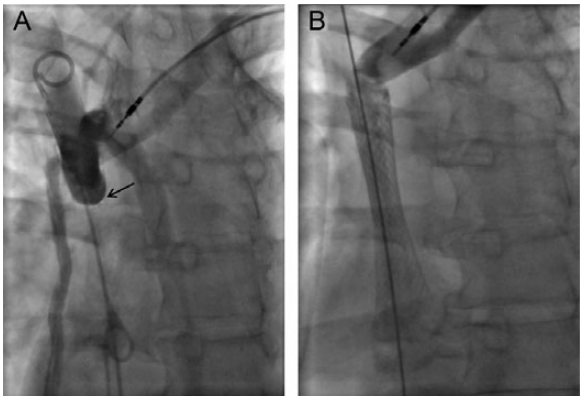
A 30-year-old woman was admitted with symptomatic bradycardia 2 weeks after undergoing a third ablation procedure for inappropriate sinus tachycardia (IST) in another centre. A permanent pacemaker was implanted. She re-presented 3 days later with swelling of both arms, neck and head consistent with superior venae cava (SVC) obstruction syndrome.

Venography showed bilateral brachiocephalic vein thrombosis extending to the SVC. There was no symptomatic improvement with therapeutic anticoagulation and repeat venography demonstrated increased thrombus load. Systemic thrombolysis was performed and subsequent venography confirmed the resolution of the thrombus but persistent SVC obstruction (*Figure A*).



A combined procedure was performed to stent the SVC and to revise the pacing system. The atrial lead was removed and the ventricular lead was withdrawn into the subclavian vein providing access to the left subclavian vein and a channel through the occlusion. Via a right femoral approach the SVC obstruction was stented with self-expanding stents (*Figure B*). A new atrial lead was inserted and the existing RV lead was advanced through the SVC stent and positioned in the right atrium and RV septum, respectively. This procedure resulted in a complete resolution of the symptoms within 12 h. Warfarin was restarted and the patient was discharged.

The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/Superior-vena-cava-syndrome.pdf.