Secondary prevention: Should it be accompanied by VT ablation or not?

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14th Annual Collingwood, Ontario, February 10 -12, 2017



Séminaire Winter Arrhythmia Annual Cardiac Arrhythmia Meeting Division of Cardiology, University of Toronto



Effect of ICDs



Sotalol

Amiodarone



VTACH Results

Kuck Lancet 2010

Summary OF VT Ablation Trials

Study	1 year		2 y	/rs
	<u>Control</u>	<u>Ablation</u>	<u>Control</u>	<u>Ablation</u>
V TACH ¹	40%	60%	30%	50%
IVTC ²		70%		
VANISH ³	50%	65%	40%	50%

VT Catheter ablation is a palliative procedure with high likelihood of recurrence

1. Kuck Lancet 2010

3. Sapp J et al NEJM 2016

2. Tung R Heart Rhythm 2015

International VT Ablation Center Collaborative

Figure 2 Kaplan–Meier estimate of ventricular tachycardia (VT) and transplant-free survival in the overall cohort.

International VT Ablation Center Collaborative

Patients were different in almost

every way

	VT recurrence within 12 months		Transplant/death w	ithin 12 months		
	Yes (N = 536)	No (N = 1525)	P value	Yes (N = 273)	No (N = 1788)	P value
Age (years)	65.0 (55.0-72.0)	64.0 (54.0-72.0)	.341	66.0 (59.0-74.0)	64.0 (54.0-72.0)	<.001
Female	81 (15.1)	184 (12.1)	.083	35 (12.8)	230 (12.9)	1
ICM	257 (47.9)	838 (55.0)	.006	147 (53.8)	948 (53.0)	.850
EF Preablation	28.0 (20.0-40.0)	35.0 (25.0-45.0)	<.001	24.0 (20.0-30.0)	35.0 (25.0-45.0)	<.001
NYHA			<.001			<.001
I	92 (18.8)	466 (32.5)		23 (8.9)	535 (32.1)	
II	193 (39.5)	525 (36.6)		71 (27.6)	647 (38.8)	
III	164 (33.5)	372 (25.9)		113 (44.0)	423 (25.4)	
IV	40 (8.2)	71 (5.0)		50 (19.5)	61 (3.7)	
ICD	487 (92.8)	1251 (84.2)	<.001	250 (94.7)	1488 (85.2)	<.001
CRT	165 (31.4)	348 (23.4)	<.001	107 (40.5)	406 (23.3)	<.001
Electrical storm	220 (43.8)	464 (32.3)	<.001	147 (57.4)	537 (31.9)	<.001
ICD shocks	344 (72.7)	869 (62.7)	<.001	176 (76.2)	1037 (63.7)	<.001
Hypertension	285 (58.8)	753 (56.4)	.407	140 (58.6)	898 (56.8)	.662
Atrial fibrillation	163 (33.5)	394 (28.7)	.052	97 (39.3)	460 (28.5)	<.001
Diabetes mellitus	128 (24.4)	305 (20.6)	.073	92 (35.4)	341 (19.5)	<.001
Chronic kidney disease	169 (31.7)	436 (28.7)	.213	126 (46.5)	479 (26.9)	<.001
Baseline creatinine	1.1 (0.9–1.5)	1.1 (0.9–1.4)	.199	1.3 (1.0–1.7)	1.1 (0.9–1.3)	<.001
Beta-Blocker	433 (81.5)	1173 (78.3)	.123	226 (83.7)	1380 (78.4)	.056
Amiodarone	283 (59.1)	737 (54.0)	.061	172 (71.1)	848 (52.9)	<.001
≥2 antiarrhythmic drugs	110 (23.0)	228 (16.7)	.003	66 (27.3)	272 (17.0)	<.001
Prior VT ablations	0.0 (0.0-1.0)	0.0(0.0-1.0)	.019	0.0 (0.0-1.0)	0.00 (0.0-1.0)	.001
Min-Max	0.0-7.0	0.0-10.0		0.0-6.0	0.0-10.0	

The Importance of VT in the ICD Era

VT is *still* associated with adverse outcomes...(or at least shocks are)

Poole NEJM 2008 SCD-HeFT substudy

Sweeney *Heart Rhythm* 2010 PainFREE Rx, PainFREE RxII, Empiric, Prepare

ATP and Shocks reduce Mortality

Data from 69,383 pts with ICDs 2008-13

ICD shocks are associated With reduced mortality

ATP is associated with reduced mortality

Substrate is assoc with reduced mortality

Elimination of VT with catheter ablation may eliminate VT

No evidence VT ablation can change mortality

Reducing Shocks

- "The combination of Long Detection Interval (LDI) and ATP during charging is extremely effective and significantly reduces appropriate but unnecessary therapies
- The use of LDI alone yielded a 39% reduction in appropriate but unnecessary therapies
- ATP on top of LDI determined another 52% reduction in unnecessary shocks"

Europace (2016) 18 (11): 1719-1725

VANISH: Methods

Randomized trial (22 sites)

Stratified by centre and Amiodarone vs Non-Amiodarone at baseline

Inclusion

- Prior MI
- ICD
- One of the Following VT Events
 - \geq 3 episodes VT treated with ATP, with symptoms
 - \geq 1 appropriate ICD shock
 - ≥ 3 VT episodes within 24 hours
 - Sustained VT below programmed ICD detection
- VT Event occurred despite antiarrhythmic drug therapy

Sapp J et al NEJM 2016

Methods: Escalated AAD Arm

Sotalol [] Amiodarone load then 200 mg/day

Amiodarone <300 [] Amio reload, then 300 mg/day

Amiodarone ≥300 mg/day [] Amio + Mexiletine 600 mg/day

Sapp J et al NEJM 2016

Methods: Catheter Ablation

- All inducible VTs targeted for ablation
- Mappable [] map and ablate
- Unmappable VTs [] substrate + pace-map
- Non-inducible or Unstable substrate/LAVA/latency
- Endpoint of no-inducible VT
- Patients remained on baseline antiarrhythmic drug therapy

Results: Primary Outcome

Composite: Death, VT Storm 30d, Appropriate Shock

Summary

- ICD is mainstay of Rx
 - No evidence VT ablation will reduce SCD, VF or any hard endpoint except VT (in some)
- Sicker patients have:
 - More VT (ATP and shocks)
 - Higher mortality
 - Lower ablation success rates
 - VT ablation does not change mortality
- Successful ablation is a marker for less sick patients
- Despite successful ablation VT often recurs
 - Adjuvant palliative therapy

Not the plumber

Results: Primary Outcome

Composite: Death, VT Storm 30d, Appropriate Shock

Results: Subgroups

_			Subgroup	Ablation	AAD	Hazard Ratio (95% C	P Value) Interac
			Baseline antiarrhythmic	r pauerns with even	notal no. of patients (%)		0.03
			Amiodarone	52/85 (61.2)	65/84 (77.4)		0.55 (0.38,0.80)
			Non-amiodarone	26/47 (55.3)	22/43 (51.2)		1.14 (0.65,2.02)
			Ejection fraction	05/55 (00.0)	40/50 (70.0)		0.20
			< 311%	15/55 / 5 1 h 1	26/59 / / X III		
							P Value to
Subaroup	Ablation	AAD	Haza	ard Ratic	o (95% CI)		Interaction
g	no of notionto with avoid	thatal na of nation	to (0/)		(interaction
	no. of patients with event	notal no. ol patient	lS (70)	1			
Baseline antiarrhyt	hmic						0.03
Baseline antiannyt			-	_			0.00
Amiodarone	52/85 (61.2)	65/84 (77.4)				0.55 (0.38	5,0.80)
Non-amiodarone	26/47 (55 3)	22/43 (51.2)				1 14 (0 65	2 02
Non-annouarone	20/47 (00.0)	22/43 (31.2)			-	1.1+ (0.00	,2.02)
			ICD shock within 3 month	S	C1/01 (7E 2)		0.76
			res	27/48 (56.3)	26/46 (56 5)		0.70 (0.46,1.02)
			Sex	21140 (00.0)	20/40 (00.0)	_	0.66
			Male	74/123 (60.2)	80/118 (67.8)		0.74 (0.54,1.01)
			Female	4/9 (44.4)	7/9 (77.8)		0.59 (0.16,2.13)
			Age				0.30
			<70 yr	47/78 (60.3)	32/53 (60.4)		0.88 (0.56,1.38)
				31/54 (57.4)	55/74 (74.3)		0.61 (0.39,0.94)
			<550 og/ml	19/40 (47.5)	23/37 (62 2)		0.63 (0.34 1.16)
)nlv cigniti	cant interaction	n was	>550 pg/ml	25/35 (71.4)	32/42 (76.2)		0.83 (0.49,1.41)
nny signin	cant interactiv		QRS duration				0.70
			<150 msec	34/63 (54.0)	35/57 (61.4)		0.80 (0.50,1.28)
ha hacalin	a antiarrhyth	min drug	<u>></u> 150 msec	41/63 (65.1)	45/61 (73.8)		0.69 (0.45,1.06)
ne baselin	e anuarrnvuni	mic arug	Index arrhythmia event	0// / (FT /)	7/00 (05.0)		0.35
			AIP	8/14 (57.1)	7/20 (35.0)		1.45 (0.52,4.01)
• •			VT storm	5/12 (41 7)	16/20 (80.0)		0.47 (0.46, 1.04)
amindaror	10 VC non-		VT below defect	18/32 (56.3)	17/26 (65.4)	_	0.66 (0.34,1.29)
annouaror			Location of MI	. ,	· · /		0.78
			Anterior	14/24 (58.3)	11/14 (78.6)		0.75 (0.45,1.28)
middaran			Not anterior	52/82 (63.4)	58/90 (64.4)		0.89 (0.61,1.29)
Iniouaron	e)		Atrial fibrillation	20/52 (57.7)	20/47 (64 7)		0.09 (0.52 1.46)
	-/		No atrial fibrillation	48/80 (60.0)	58/80 (72.5)		0.65 (0.53, 1.46)
			No dala institution	40/00 (00.0)	00/00 (12:0)	_	0.00 (0.11,0.00)
			All patients				0.72 (0.53,0.98)
					0.1 0.2	0.5 1 2	5 10
					Ablatio	on Better AA	D Better
					Ablatio	on Better AA	► D Better

Results: Baseline antiarrhythmic drug strata

Treatment-Attributable Adverse Events

Event	AAD Group (n=127) No. (%)	Catheter Ablation Group (n=132) No. (%)	Р
atheter Ablation Related			
Vascular injury		3 (2.3)	0.25
Major Bleeding	1 (0.8)	3 (2.3)	0.62
Cardiac Perforation	1 (0.8)	2 (1.5)	1.00
Endocarditis	1 (0.8)		0.49
Heart Block	1 (0.8)		0.49
i tiarrhythmic Drug Related Death			
Pulmonary toxicity	2 (1.6)		0.24
Liver toxicity/multiorgan failure	1 (0.8)		0.49
Pulmonary Infiltrate	2 (1.6)		0.24
Shortness of Breath Heart Failure Admission	3 (2.4)	1 (0.8)	0.36
Hyperthyroidism	5 (3.9)	3 (2.3)	0.49
Hypothyroidism	5 (3.9)	2 (1.5)	0.27
Hepatic Dysfunction	6 (4.7)		0.013
Tremor/Ataxia	6 (4.7)		0.013
SFX Leading To Drug Therapy Change	6 (4.7)		0.013
Other adverse events no. (%)	6 (4,7)	4 (3.0)	0.53

Conclusion

Catheter ablation is superior to escalation of antiarrhythmic drug therapy...

WHEN AMIODARONE FAILS

...for reducing the combined endpoint of death, appropriate shock, and VT storm, driven by reductions in VT storm and shock.

Priorities for 2° Prevention

- 1. ICD with Painfree II / appropriate programming
- If VT... start amiodarone
 (Sotalol can be used an intermediate step if good EF)

- If VT on Amio (slower and better tolerated) ... Or S/E on Amio (needs discontinuation) ... catheter ablation...
- 4. Repeat catheter ablation...

Next Steps

VANISH-2 Pilot Study

	Antiarrhythmic Drug N=127	Catheter Ablation N=132
Age (yr)	70.3 ± 7.3	67.0 ±8.6
Male	118 (92.9%)	123 (93.2%)
Diabetes—no.(%)	40 (31.5)	37 (28.0)
Hypertension -no.(%)	88 (69.3)	92 (69.7)
Renal Insufficiency -no.(%)	26 (20.5)	23 (17.4)
Atrial Fibrillation or Atrial flutter – no.(%)	47 (37.0)	52 (39.4)
Functional Class		
NYHA FC I -no.(%)	28 (22.0)	33 (25.0)
NYHA FC II -no.(%)	68 (53.5)	69 (52.3)
NYHA FC III –no.(%)	31 (24.4)	30 (22.7)

	Antiarrhythmic Drug N=127	Catheter Ablation N=132
Ejection Fraction—%	31.2 ± 10.7	31.1 ± 10.4
Single Chamber ICD—no.(%)	44 (34.7)	43 (32.6)
Dual Chamber ICD—no.(%)	61 (48.0)	60 (45.5)
CRT Defibrillator—no.(%)	22 (17.3)	29 (22.0)
Estimated GFR (Cockroft-Gault)	70.2 ± 26.4	75.8 ± 29.0
Sodium (mmol/L)	138.4 ± 3.4	138.5 ± 3.0
Potassium (mmol/L)	4.3 ± 0.4	4.3 ± 0.4
NT-proBNP (pg/mL)	937.3 ± 895.5	1010.3 ± 1252.7

	Antiarrhythmic Drug N=127	Catheter Ablation N=132
Antiarrhythmic Drug At Time of Qualification:		
Non Amiodarone – no.(%)	43 (33.9)	47 (35.6)
Sotalol – no.(%)	43 (33.9)	46 (34.8)
Procainamide – no.(%)	0	1 (0.76)
Amiodarone-no.(%)	84 (66.1)	85 (64.4)
Dose < 300 mg/day	73 (57.5)	77 (58.3)
Dose ≥300 mg/day -no.(%)	11 (8.7)	8 (6.1)

	Antiarrhythmic Drug N=127	Catheter Ablation N=132
Other Medications		
Beta-blocker – no.(%)	122 (96.1)	124 (93.9)
ACE Inhibitor –no.(%)	83 (65.4)	86 (64.4)
ARB –no.(%)	28 (22.1)	31 (23.5)
Diuretic - no.(%)	89 (70.1)	90 (68.2)
Digoxin – no.(%)	25 (19.7)	27 (20.5)
Aspirin – no.(%)	85 (75.9)	99 (83.9)
Calcium channel blocker – no.(%)	19 (15.0)	14 (10.6)
Warfarin – no.(%)	42 (37.5)	47 (39.5)
Non-warfarin anticoagulant –no.(%)	12 (9.5)	11 (8.3)

Results: Components of Primary Outcome

Pending Studies

This is a very difficult area to study

- CEASE-VT
- ASPIRE
- CALYPSO
- STAR-VT

CONTEMPORARY REVIEW

Catheter ablation of ventricular tachycardia: Lessons learned from past clinical trials and implications for future clinical trials

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VANISH2 Pilot: Funding

- Biosense Webster
- St. Jude Medical

• Heart and Stroke Foundation

Need for the trial

- National survey
- Named as a priority in multiple consensus documents (2006 AHA/ACC/ESC; 2009 HRS/EHRA; 2014 EHRA/HRS/APHRS)
- Patient Focus Groups

Trial Design

Sample size

- Pilot: 75 patients
- Main trial 330 patients

Acknowledgements

Executive Committee: John L. Sapp, Anthony S. Tang, George A. Wells, Ratika Parkash, William G. Stevenson

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Sotalol

Amiodarone

Side-effects

Long-term amiodarone treatment (CIDS f/u)

82% of pts had amio SFX 50% requiring dose reduction 22% serious

Bokhari Circulation, 2004

VT Reduction: Catheter Ablation

Stevenson

VT is a result of disease of *PART* of the myocardium

Thermocool Study

Stevenson et al, Circulation, 2008

Survival Curve

Ablation Evidence And Trials

Randomized Trials

- SMASH-VT (Reddy NEJM 2007)
- V-Tach (Kuck Lancet 2010)

Ablation vs Amiodarone Antiarrhythmic Drug naive

Ablation vs no therapy

VANISH Trial

- Multicentre, multinational randomized trial (22 sites)
- Canadian Institutes of Health Research
- Unrestricted Research Grants: St. Jude Medical, Biosense Webster

VANISH: Methods

Exclusion

- Unable to consent
- Acute coronary syndrome, MI, or other reversible cause of VT
- Ineligible to take amiodarone or mexiletine
- Ineligible for catheter ablation
- Severe renal failure, functional class IV dyspnea or angina, pregnancy, estimated survival < 1 year
- Prior catheter ablation for VT

- Standardized ICD Programming and f/u
- Blinded adjudication of endpoints
- Primary Outcome:
 - Death
 - Appropriate ICD shock after 30 days
 - VT Storm after 30 days

VANISH: Results

Catheter Ablation Procedural Characteristics

	Catheter Ablation	Antiarrhythmic
	Group†	Drug Group†
Number of Procedures	158	66
Mapping Methods used		
Activation Mapping	59 (37.3)	33 (50.0)
Entrainment Mapping	50 (31.6)	30 (60.0)
Substrate Mapping	140 (88.6)	57 (86.4)
Pace-Mapping	116 (73.4)	52 (78.8)
No Inducible Arrhythmia at Baseline	14	4
RF Time (minutes)	38.7 ± 21.9	36.8 ± 20.6
Number of RF applications	29.4 ± 27.9	38.9 ± 26.7
Fluoroscopy time (minutes)	31.5 ± 20.8	29.4 ± 35.1
Procedure time (minutes)	263 ± 83.5	251 ± 85.0
Reinduction Testing Performed	130 (82.2)	52 (78.8)
Acutely Successful Procedure*	110	33

+ Plus-minus values represent mean ± SD; categorical values are n (%). * Acute success was defined to include procedures in which reinduction testing was performed, and no arrhythmia was inducible or only nonclinical VT with CL<300 msec was inducible.

Causes Of Death

Event	AAD Group (n=127) No. (%)	Catheter Ablation Group (n=132) No. (%)	Р
Death	35 (27.6)	36 (27.3)	1.0
Non-Cardiac Death	8 (6.3)	12 (9.1)	0.49
Cardiovascular Death	26(20.5)	24(18.2)	0.75
Myocardial Infarction		1 (0.8)	1.0
Congestive Heart Failure	19 (15.0)	17 (12.9)	0.72
Ventricular Arrhythmia	5 (3.9)	3 (2.3)	0.50
Stroke		1 (0.8)	1.0
Other Cardiovascular	1 (0.8)		0.49
ICD-Related Death	2 (1.6)	2 (1.5)	1.0
Unknown Cause of Death	1 (0.8)		0.49

Limitations

- Not powered to assess mortality
- Multicentre trial, operator-dependence
- Potential impact of prolonged detection time

Discussion

High risk population:

~50% recurrence and ~25% mortality at 3 years Most deaths due to heart failure or non-cardiac causes

 A significant difference in mortality was not observed

Discussion

- Most of the benefit was observed among patients with VT despite amiodarone.
- Adverse events tended to be more frequent among patients treated with escalated antiarrhythmic drug therapy.

International VT Ablation Center Collaborative

Figure 1 Kaplan–Meier estimate of freedom from ventricular tachycardia (VT) in the overall cohort.

Effect of ICDs

Drugs and Ablation for <u>VT</u> Reduction

SMASH-VT: ICD Therapy

SMASH-VT:	ICD Therapy	y
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The NEW ENGLAND JOURNAL of MEDICINE			
ESTABLISHED IN 1812 DECEMBER 27, 2007 VOL. 357 NO. 26			
Prophylactic Catheter Ablation for the Prevention of Defibrillator Therapy			
Vivek Y. Reddy, M.D., Matthew R. Reynolds, M.D., Petr Neuzil, M.D., Ph.D., Allison W. Richardson, M.D., Milos Taborsky, M.D., Ph.D., Krit Jongnarangsin, M.D., Stepan Kralovec, Lucie Sediva, M.D., Jeremy N. Ruskin, M.D., and Mark E. Josephson, M.D.			

3-Center RCT, 128 patients with VT/VF being implanted with ICD (also included some pts with therapy from primary prophylactic ICD) Excluded VT storm and recurrent VT

Randomized to prophylactic VT ablation vs ICD alone

SMASH-VT: ICD Therapy

VTACH

Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): a multicentre randomised controlled trial

Karl-Heinz Kuck, Anselm Schaumann, Lars Eckardt, Stephan Willems, Rodolfo Ventura, Etienne Delacrétaz, Heinz-Friedrich Pitschner, Josef Kautzner, Burghard Schumacher, Peter S Hansen, for the VTACH study group*

Summary

Background In patients with ventricular tachycardia (VT) and a history of myocardial infarction, intervention with an implantable cardioverter defibrillator (ICD) can prevent sudden cardiac death and thereby reduce total mortality. However, ICD shocks are painful and do not provide complete protection against sudden cardiac death. We assessed the potential benefit of catheter ablation before implantation of a cardioverter defibrillator.

Lancet 2010; 375: 31–40 See Comment page 4 *Members listed at end of paper Hanseatisches Herzzentrum, Asklepios Klinik St Georg,

RCT of patients with stable VT (no syncope, BP >90) to receive either ICD <u>or</u> ICD and ablation

110 pts; 54 randomized to ablation, 8 not ablated (1 excluded, 2 had complications precluding ablation, 5 had technical problems or access issues etc)

A group with higher risk of recurrent VT

Lancet 2010