

Sindrome di Brugada nel Paziente Asintomatico Il Punto della Situazione

Riccardo Cappato, MD

Arrhythmia & Electrophysiology Center
IRCCS - MultiMedica Group, Milan, Italy

Disclosure Statement of Financial Interest

- Consultant to: Boston Scientific; Medtronic; Biosense Webster; Boehringer Ingelheim; Bayer HealthCare; Abbott; Pfizer
- Speaker's Bureau: Boston Scientific; Medtronic; Biosense Webster; Sanofi; Boehringer Ingelheim; Bayer HealthCare; Abbott
- Investigator: Medtronic; Biosense Webster; Sanofi; Cameron Health; Bayer HealthCare; Abbott; Pfizer
- Grants: Boston Scientific; Medtronic; Biosense Webster
- Equity and Intellectual Property Rights: Cameron Health; Atacor Inc; 1 WorldVista; Norma AF

Brugada Syndrome in Asymptomatic Patients: Where Are We?

Preamble

- The prevalence of type-I ECG pattern in the general population is estimated to be 0.05% (1 in 5,000-10,000 individuals)

Brugada Syndrome in Asymptomatic Patients: Where Are We?

Baseline assumption

- Patients with spontaneous type-I ECG pattern in V₁-V₂ leads carry an inherently increased risk of sudden death compared to patients without such finding

Brugada Syndrome in Asymptomatic Patients: Where Are We?

Investigation methods

- Selection of the asymptomatic individual represents the ideal target to investigate the intrinsic nature of the disease, as it provides
 - risk recognition before onset of symptoms
 - delivery of preventive therapies

Brugada Syndrome in Asymptomatic Patients: Where Are We?

Investigation methods

- Given the ominous outcome (sudden death) possibly expected in asymptomatic carriers of spontaneous type-I ECG pattern, preventive therapy appears unpostponable once the diagnosis has been made

Brugada Syndrome in Asymptomatic Patients: Where Are We?

Proposed therapies

- Drug treatment
- Implantable cardioverter defibrillators
- Catheter ablation

Brugada Syndrome in Asymptomatic Patients: Where Are We?

Proposed therapies

- While preventive therapies appear intuitive in symptomatic patients, their administration in asymptomatic carriers of type-I ECG pattern raises insecurity
- General practitioners retain the concept that individuals with this finding are at higher risk of sudden death than non-carriers (i.e., general population), but do not really know what to do with this information
- As a consequence, practitioners use to refer these individuals to third-level referring centers

Brugada Syndrome in Asymptomatic Patients: Where Are We?

Proposed therapies

- While preventive therapies appear intuitive in symptomatic patients, their administration in asymptomatic carriers of type-I ECG pattern raises insecurity
- General practitioners retain the concept that individuals with this finding are at higher risk of sudden death than non-carriers (i.e., general population), but do not really know what to do with them
- As a consequence, practitioners use to refer these individuals to third-level referring centers
 - Drug treatment
 - Implantable cardioverter defibrillators
 - Catheter ablation

Brugada Syndrome in Asymptomatic Patients: Where Are We?

Brugada syndrome in perspective

- Patients with spontaneous type-I ECG pattern in V₁-V₂ leads carry an inherently increased risk of sudden death compared to patients without such finding

Brugada Syndrome in Asymptomatic Patients: Where Are We?

Brugada syndrome in perspective

- Patients with spontaneous type-I ECG pattern in V₁-V₂ leads carry an inherently increased risk of sudden death compared to patients without such finding

Is this assumption evidence-based?

Brugada Syndrome in Asymptomatic Patients: Where Are We?

Brugada syndrome in perspective

- Patients with spontaneous type-I ECG pattern in V₁-V₂ leads carry an inherently increased risk of sudden death compared to patients without such finding

Prerequisites

Brugada Syndrome in Asymptomatic Patients: Where Are We?

Brugada syndrome in perspective

- Patients with spontaneous type-I ECG pattern in V₁-V₂ leads carry an inherently increased risk of sudden death compared to patients without such finding

Prerequisites

Individuals/patients with
spontaneous type-I ECG pattern
(study group)



Natural course



All-cause mortality

Brugada Syndrome in Asymptomatic Patients: Where Are We?

Brugada syndrome in perspective

- Patients with spontaneous type-I ECG pattern in V₁-V₂ leads carry an inherently increased risk of sudden death compared to patients without such finding

Prerequisites

Individuals/patients with
spontaneous type-I ECG pattern
(study group)



Natural course



All-cause mortality

Individuals/patients without
spontaneous type-I ECG pattern
(control group)



Natural course



All-cause mortality

Brugada Syndrome in Asymptomatic Patients: Where Are We?

Brugada syndrome in perspective

- Patients with spontaneous type-I ECG pattern in V₁-V₂ leads carry an inherently increased risk of sudden death compared to patients without such finding

Prerequisites

Individuals/patients with
spontaneous type-I ECG pattern
(study group)



Natural course



All-cause mortality

>>>>>

Individuals/patients without
spontaneous type-I ECG pattern
(control group)



Natural course

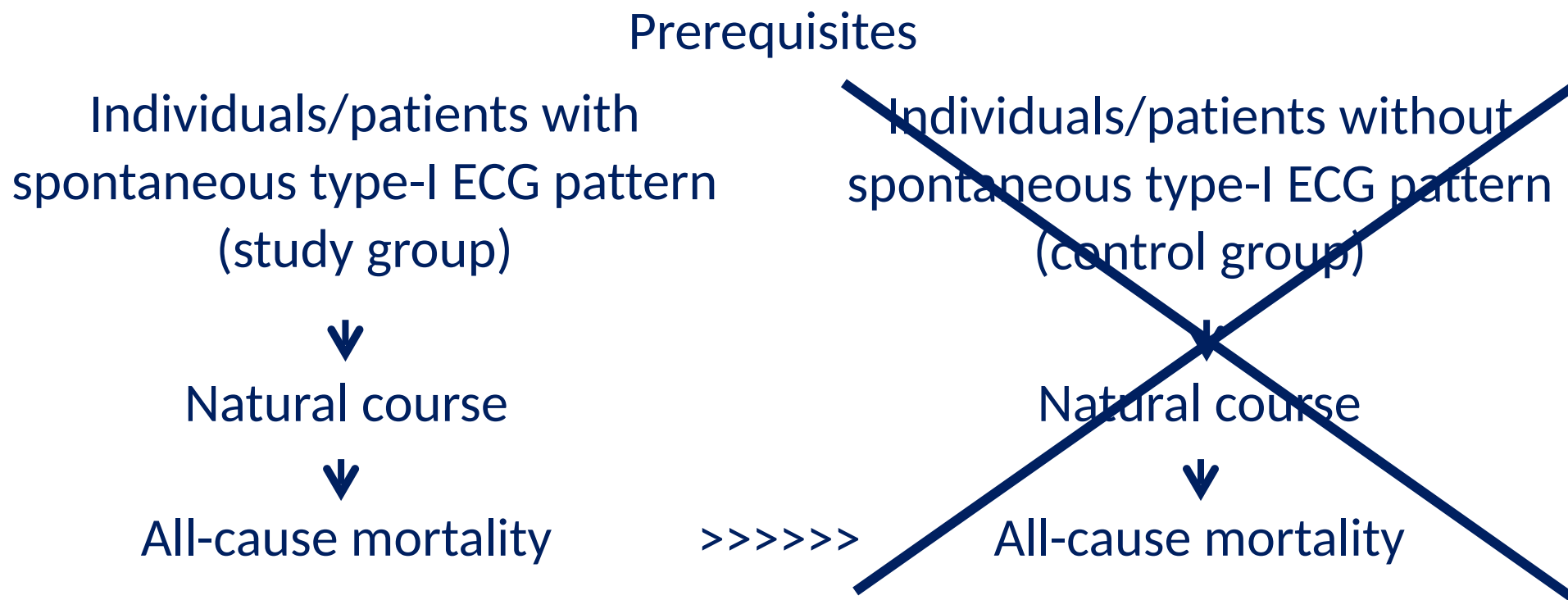


All-cause mortality

Brugada Syndrome in Asymptomatic Patients: Where Are We?

Brugada syndrome in perspective

- Patients with spontaneous type-I ECG pattern in V₁-V₂ leads carry an inherently increased risk of sudden death compared to patients without such finding



Brugada Syndrome in Asymptomatic Patients: Where Are We?

Brugada syndrome in perspective

- Patients with spontaneous type-I ECG pattern in V₁-V₂ leads carry an inherently increased risk of sudden death compared to patients without such finding

Prerequisites

Individuals/patients with
spontaneous type-I ECG pattern
(study group)



Natural course



All-cause mortality

~~Individuals/patients without
spontaneous type-I ECG pattern
(control group)~~

~~Natural course~~



~~All-cause mortality~~

>>>>>

Studies with control populations not available!

How Did We Come to the Belief that Type-I ECG Pattern Indicates a “Higher” Risk of Sudden Death?

Brugada Syndrome in Asymptomatic Patients: Where Are We?

How did we come to the belief

1. The original sin
2. Metodology of literature data source

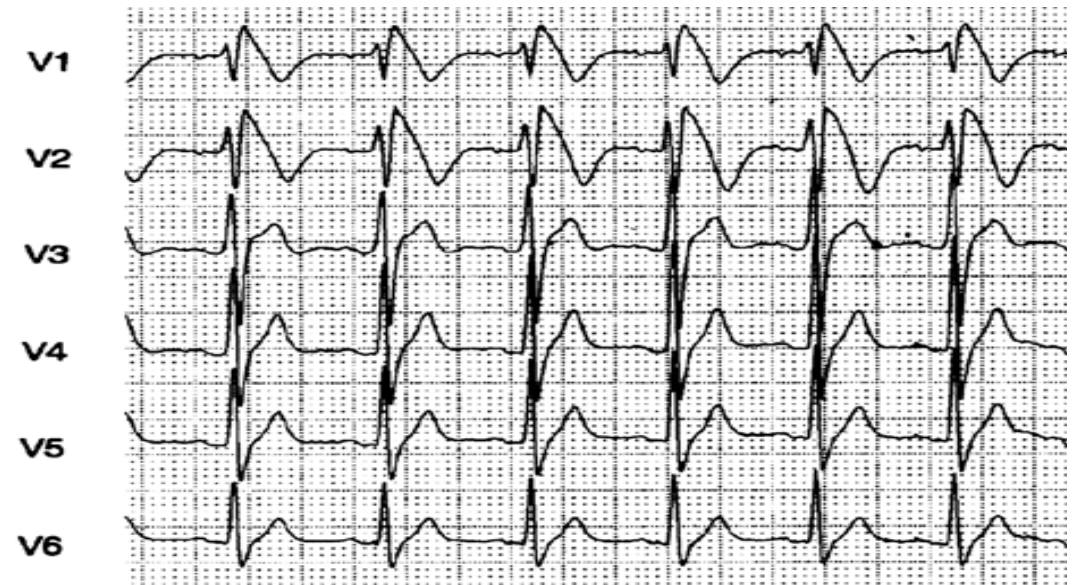
The Original Sin

Brugada Syndrome in Asymptomatic Patients: Where Are We?

The original sin

Seminal reports

- First patient identified in 1986
- First abstract including 4 patients in 1991 (Brugada P, Brugada J. PACE)
- First article including 8 patients in 1992 (Brugada P, Brugada J. JACC;20,1391-6)

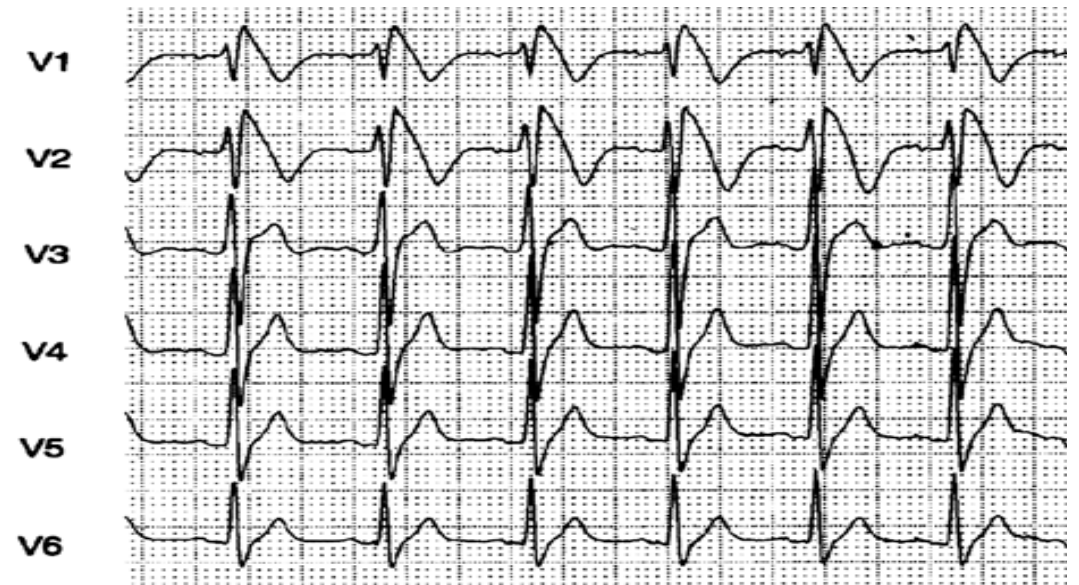


Brugada Syndrome in Asymptomatic Patients: Where Are We?

The original sin

Seminal reports

- First patient identified in 1986
- First abstract including 4 patients in 1991 (Brugada P, Brugada J. PACE)
- First article including 8 patients in 1992 (Brugada P, Brugada J. JACC;20,1391-6)



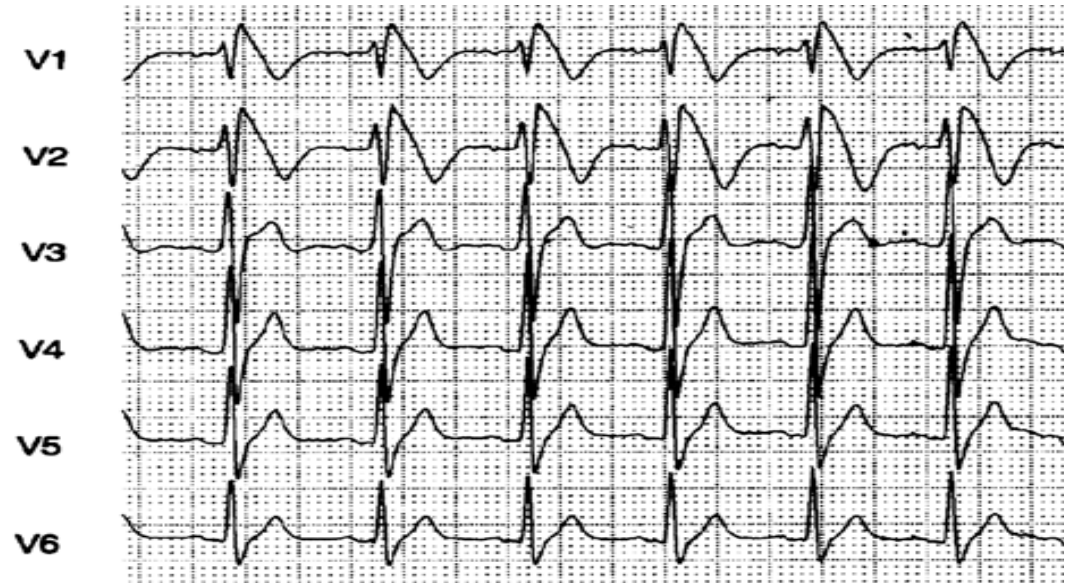
→ evidence: ST-segment elevation in V1-V2 is associated with
SD

Brugada Syndrome in Asymptomatic Patients: Where Are We?

The original sin

Seminal reports

- First patient identified in 1986
- First abstract including 4 patients in 1991 (Brugada P, Brugada J. PACE)
- First article including 8 patients in 1992 (Brugada P, Brugada J. JACC;20,1391-6)



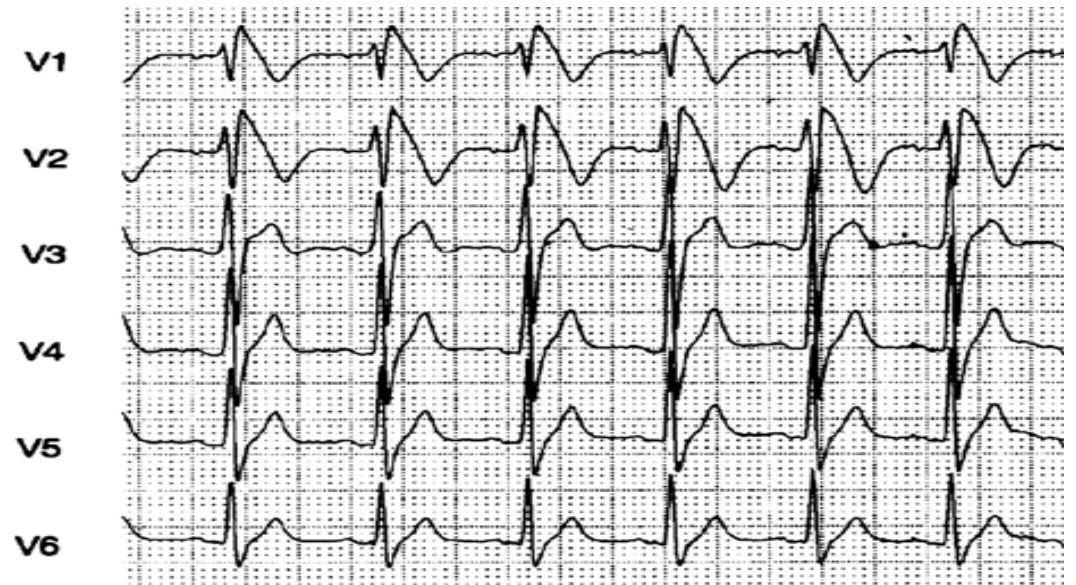
- evidence: ST-segment elevation in V1-V2 is associated with SD
- interpretation: ST-segment elevation in V1-V2 is the cause of SD

Brugada Syndrome in Asymptomatic Patients: Where Are We?

The original sin

Seminal reports

- First patient identified in 1986
- First abstract including 4 patients in 1991 (Brugada P, Brugada J. PACE)
- First article including 8 patients in 1992 (Brugada P, Brugada J. JACC;20,1391-6)



→ evidence: ST-segment elevation in V1-V2 is associated with

SD

→ interpretation: ST-segment elevation in V1-V2 is the cause of SD

Methodology of Literature Data Source

Efficacy of Endocardial Ablation of Drug-Resistant Ventricular Fibrillation in Brugada Syndrome Long-Term Outcome

Ahmed Karim Talib, MD, PhD et al

(Circ Arrhythm Electrophysiol. 2018;e005631)

- 123 symptomatic Brugada syndrome patients
- Spontaneous type-I ECG pattern in 391 (71%), drug-induced in 156 (29%)
- Syncope in 124 (23%)
- SD from VF in 45 (8%)
- At multivariate analysis, predictors: inducibility of sust VA and hystory of syncope

Brugada Syndrome in Asymptomatic Patients: Where Are We?

Methodology of literature data source

Syncope, aborted sudden death, etc → presence of type-I ECG pattern

Brugada Syndrome in Asymptomatic Patients: Where Are We?

Methodology of literature data source



Brugada Syndrome in Asymptomatic Patients: Where Are We?

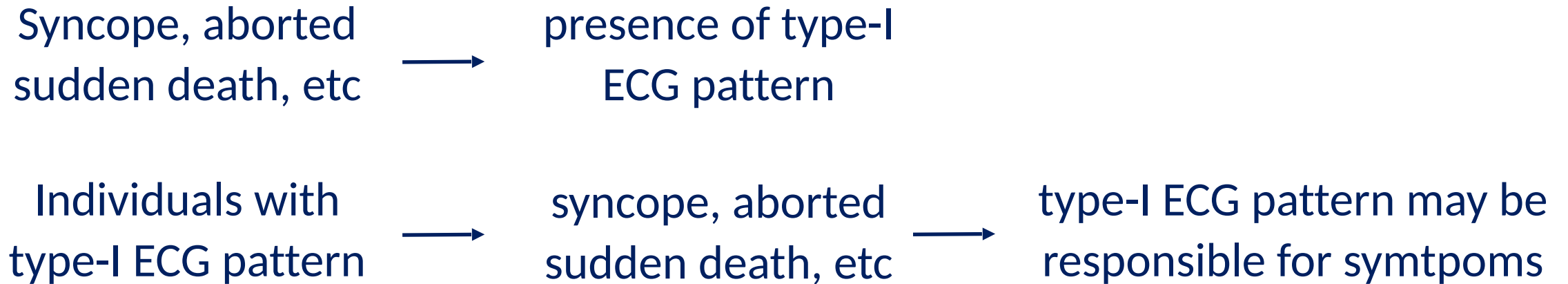
Methodology of literature data source

Syncope, aborted sudden death, etc → presence of type-I ECG pattern

Individuals with type-I ECG pattern → syncope, aborted sudden death, etc

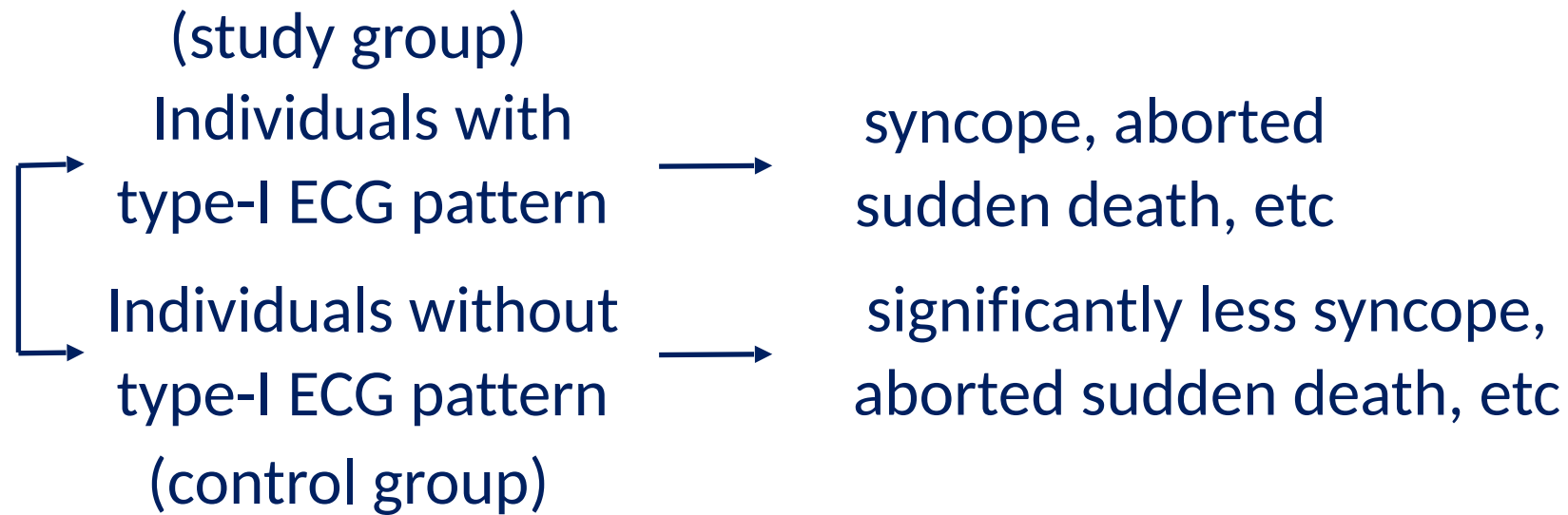
Brugada Syndrome in Asymptomatic Patients: Where Are We?

Methodology of literature data source



Brugada Syndrome in Asymptomatic Patients: Where Are We?

Methodology of literature data source



Brugada Syndrome in Asymptomatic Patients: Where Are We?

Brugada syndrome in perspective

- Patients with spontaneous type-I ECG pattern in V₁-V₂ leads carry an inherently increased risk of sudden death compared to patients without such finding

Prerequisites

Individuals/patients with
spontaneous type-I ECG pattern
(study group)



Natural course



All-cause mortality

Brugada Syndrome: What Have We Learned?

Asymptomatic subjects with type-I ECG pattern

Brugada Syndrome: What Have We Learned?

Asymptomatic subjects with type-I ECG pattern

- SD events in 6 of 539 individuals during 5-11 year FU (0.16% per year, 95% CI: 0.00%-0.5%)

Brugada Syndrome: What Have We Learned?

Asymptomatic subjects with type-I ECG pattern

- SD events in 6 of 539 individuals during 5-11 year FU (0.16% per year, 95% CI: 0.00%-0.5%) Not overly different from general population

Brugada Syndrome: What Have We Learned?

Asymptomatic subjects with type-I ECG pattern

- SD events in 6 of 539 individuals during 5-11 year FU (0.16% per year, 95% CI: 0.00%-0.5%)
- Age at time of first SD event, 57 ± 12 years

Brugada Syndrome: What Have We Learned?

Asymptomatic subjects with type-I ECG pattern

- SD events in 6 of 539 individuals during 5-11 year FU (0.16% per year, 95% CI: 0.00%-0.5%)
- Age at time of first SD event, 57 ± 12 years

Juvenile syndrome?

Brugada Syndrome: What Have We Learned?

Asymptomatic subjects with type-I ECG pattern

- SD events in 6 of 539 individuals during 5-11 year FU (0.16% per year, 95% CI: 0.00%-0.5%)
- Age at time of first SD event, 57 ± 12 years
- No data on necropsy

Brugada Syndrome: What Have We Learned?

Asymptomatic subjects with type-I ECG pattern

- SD events in 6 of 539 individuals during 5-11 year FU (0.16% per year, 95% CI: 0.00%-0.5%)
- Age at time of first SD event, 57 ± 12 years
- No data on necropsy

Arrhythmic death in the setting of an underlying disease?

Brugada Syndrome: What Have We Learned?

Summary

- Is type-I ECG pattern a marker of an underlying condition exposing carriers to an excess risk of sudden death or an incidental finding?
- At present, conclusive evidence in favor of any of the two possible conditions is missing

Brugada Syndrome: What Have We Learned?

Challenge

- Can drug or ICD treatment be proven as preventive measure to reduce the risk of sudden death in type-I ECG pattern carriers?

Brugada Syndrome: What Have We Learned?

Challenge

- Can drug or ICD treatment be proven as preventive measure to reduce the risk of sudden death in type-I ECG pattern carriers?
 - incidence rate of sudden death very low,
 - large patient volumes required to randomize treatment versus no treatment

Brugada Syndrome: What Have We Learned?

Challenge

- Can drug or ICD treatment be proven as preventive measure to reduce the risk of sudden death in type-I ECG pattern carriers?
 - incidence rate of sudden death very low,
 - large patient volumes required to randomize treatment versus no treatment
- What is the difference in "ablating" patients with frequent PVCs or VT/VF and type-I ECG pattern versus patients with the same arrhythmias and no type-I ECG pattern?

Brugada Syndrome: What Have We Learned?

Challenge

- Can drug or ICD treatment be proven as preventive measure to reduce the risk of sudden death in type-I ECG pattern carriers?
 - incidence rate of sudden death very low,
 - large patient volumes required to randomize treatment versus no treatment
- What is the difference in "ablating" patients with frequent PVCs or VT/VF and type-I ECG pattern versus patients with the same arrhythmias and no type-I ECG pattern?
 - no control studies available

Brugada Syndrome: What Have We Learned?

Conclusions

- At present, no conclusive evidence available with respect to the independent risk of sudden death associated with type-I ECG pattern
- Demonstration of such risk is difficult to be obtained and requires more rigorous, epidemiologically sound science applied
- Such methodology is required both for asymptomatic and symptomatic patients with type-I ECG pattern

Brugada Syndrome: What Have We Learned?

5. Control groups in published studies

1. Surviving a VF episode

(risk of recurrent VT/VF requiring ICD therapy)

Brugada
Syndrome
* 0.6%/month

Idiopathic VF
Up to 1%/month

Brugada Syndrome: What Have We Learned?

5. Control groups in published studies

	Brugada Syndrome	General Population	Idiopathic VF
1.Surviving a VF episode (risk of recurrent VT/VF requiring ICD therapy)	* 0.6%/month		# Up to 1%/month
2.Natural course (risk of first VF)			

Brugada Syndrome: What Have We Learned?

5. Control groups in published studies

	Brugada Syndrome	General Population	Idiopathic VF
1.Surviving a VF episode (risk of recurrent VT/VF requiring ICD therapy)	0.6%/month		Up to 1%/month
2.Natural course (risk of first VF)	* 0.16%/year		

* Gaita et al, 2024

Brugada Syndrome: What Have We Learned?

5. Control groups in published studies

	Brugada Syndrome	General Population	Idiopathic VF
1.Surviving a VF episode (risk of recurrent VT/VF requiring ICD therapy)	0.6%/month		Up to 1%/month
2.Natural course (risk of first VF)	* 0.16%/year	# 0.14%/year	

* Gaita et al, 2024

Mizusawa et al, 2012