

Reply by Casella et al to Letter Regarding Article, “Incidence of ventricular arrhythmias related to Covid infection and vaccination in patients with Brugada syndrome: Insights from a large Italian multicenter registry based on continuous rhythm monitoring”

Michela Casella¹, Sergio Conti², Paolo Compagnucci³, Valentina Ribatti⁴, Maria Lucia Narducci⁵, Lorenzo Marcon⁶, Francesca Massara¹, Yari Valeri³, Luca De Francesco⁷, Annamaria Martino⁸, Chiara Ghiglieri⁹, Marco Schiavone¹⁰, Cristina Balla¹¹, Gabriele Dell’Era¹², Gemma Pelargonio¹³, Giovanni Battista Forleo¹⁰, Saverio Iacopino¹⁴, Giuseppe Sgarito¹⁵, Leonardo Calò⁸, Claudio Tondo¹⁶, Antonio Dello Russo¹, and Giuseppe Patti⁹

¹Ospedali Riuniti Ancona Umberto I-G.M. Lancisi-G. Salesi

²ARNAS Civico Di Cristina Benfratelli

³Marche University Hospital

⁴Centro Cardiologico Monzino

⁵Università Cattolica del Sacro Cuore Facoltà di Medicina e Chirurgia

⁶Monzino Cardiology Centre

⁷Fondazione Policlinico Universitario Agostino Gemelli IRCCS

⁸Policlinico Casilino

⁹University Hospital Maggiore della Carità

¹⁰Luigi Sacco University Hospital

¹¹Azienda Ospedaliera Universitaria di Ferrara, Cona (FE)

¹²Azienda Ospedaliera Universitaria Maggiore della Carità

¹³Università Cattolica del Sacro Cuore Sede di Roma

¹⁴Villa Maria Cecilia

¹⁵Ospedali Civico e Benfratelli

¹⁶Centro Cardiologico Monzino Istituto di Ricovero e Cura a Carattere Scientifico

June 19, 2023

Reply by Casella et al to Letter Regarding Article,

Incidence of ventricular arrhythmias related to Covid infection and vaccination in patients with Brugada syndrome: Insights from a large Italian multicenter registry based on continuous rhythm monitoring.

Michela Casella^{1,2}, MD, PhD, Sergio Conti³, MD, PhD, Paolo Compagnucci^{1,4}, MD, Valentina Ribatti⁵, MD, PhD, Maria Lucia Narducci⁶, MD, PhD, Lorenzo Marcon⁵, MD, Francesca Massara¹, MD, Yari Valeri¹, MD, Luca De Francesco⁶, MD, Anna Maria Martino⁷, MD, PhD, Chiara Ghiglieri⁸, MD, Marco Schiavone⁹, MD, Cristina Balla¹⁰, MD, Gabriele Dell’Era⁸, MD, Gemma Pelargonio⁶, MD, PhD Giovanni Battista Forleo⁹, MD, PhD, Saverio Iacopino¹¹, MD, Giuseppe Sgarito³, MD, PhD, Leonardo Calò⁷, MD, FESC, Claudio Tondo^{5,12}, MD, PhD, Antonio Dello Russo^{1,4}, MD, PhD, Giuseppe Patti⁸, MD

1. Cardiology and Arrhythmology Clinic, University Hospital Ospedali Riuniti Umberto I-Lancisi-Salesi, Ancona, Italy.
2. Department of Clinical, Special and Dental Sciences, Marche Polytechnic University, Ancona, Italy.
3. Department of Electrophysiology, ARNAS Civico – Di Cristina – Benfratelli, Palermo, Italy.
4. Department of Biomedical Science and Public Health, Marche Polytechnic University, Ancona, Italy.
5. Centro Cardiologico Monzino IRCCS, Milan, Italy.
6. Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy.
7. Department of Cardiology, Policlinico Casilino, Rome, Italy.
8. Division of Cardiology, University Hospital Maggiore della Carità, University of Eastern Piedmont, Novara, Italy.
9. Arrhythmology, Luigi Sacco Hospital, Milan, Italy.
10. Cardiovascular Institute, Azienda Ospedaliero-Universitaria di Ferrara, Cona (FE), Italy.
11. Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy.
12. Department of Biomedical, Surgery and Dental Sciences, University of Milan, Milan, Italy.

Corresponding author:

Sergio Conti, MD, PhD

ARNAS Civico, Department of Cardiac Electrophysiology

P.zza Nicola Leotta, 4 – 90127 Palermo, Italy

Tel: (+39)0916665038; mail: sergioconti.md@gmail.com

We thank Dr. Dendramis and Dr. Brugada for their interest in our paper [1].

Overall, our population included a large and non-selected cluster of patients previously diagnosed with Brugada syndrome (BrS). That said, 50.3% of patients in our analysis (164/326 patients) had a spontaneous Brugada type 1 electrocardiogram (ECG). It is well-demonstrated that patients with a spontaneous Brugada type 1 ECG have a worse arrhythmic prognosis than patients with drug-induced Brugada type 1 ECG [2]. Previous data from large meta-analyses reported an arrhythmic risk three to four times higher in asymptomatic patients with a spontaneous Brugada type 1 ECG [3,4]. In addition, 20.1% of patients presenting with a spontaneous type 1 ECG also had a history of documented ventricular fibrillation/sudden cardiac death (VF/SCD), thus representing an even higher risk population. In our population, 10.4% of patients had a previous history of VF/SCD documented. Patients with a history of severe ventricular arrhythmias or aborted SCD are considered at high risk, with an estimated recurrence rate of arrhythmic events of 48% over ten years [5].

Among the group of patients with drug-induced Brugada type 1 ECG (162/326 patients, 49.7%), who are generally considered at lower risk than subjects with spontaneous type 1 ECG, 23.4% had a positive programmed electrical stimulation (PES). Although we acknowledge that the role of PES in the risk stratification of asymptomatic patients remains controversial, it may still have a role in selected patients [7].

Considering only the ICD carriers (202/326 patients), the overall number of patients that presented with ventricular arrhythmias in our population was comparable between patients deemed at high risk and those at low risk. During COVID infection, 1.4% of patients with drug-induced Brugada type 1 had ventricular arrhythmias compared to 1.5% of patients with spontaneous Brugada type 1. After the first and booster vaccine dose, no sustained ventricular arrhythmias were recorded in patients with drug-induced Brugada type 1 and spontaneous Brugada type 1. After the second dose of vaccine, one VT episode was recorded in the group of patients with spontaneous Brugada type 1 and one in the group of patients with drug-induced Brugada type 1.

What surprised us the most was the peculiar timing of implantable cardioverter-defibrillator (ICD) interventions. Indeed, in the two patients that received ICD therapies (1 ATP and 1 shock), these episodes were not related to acute infection or vaccine-related hyperpyrexia but happened in the last window of the study

observation (6 months after COVID infection or 1-month after the last dose of vaccine). Moreover, one of the two episodes was in a patient with drug-induced Brugada type 1 ECG, and the other was in a subject with spontaneous Brugada type 1 ECG and positive PES.

In our opinion, the added value of our study was the extensive use of remote device monitoring and the vast amount of data collected and analyzed to assess the arrhythmic burden, which strengthen our findings. Finally, in this real-world analysis, we found that most BrS patients followed the recommendations given for fever treatment and pre-treatment. This may reconcile the apparent discrepancy between the heterogeneous risk profile and the low observed incidence of ventricular arrhythmia in our population.

References

1. Casella M, Conti S, Compagnucci P, Ribatti V, Narducci ML, Marcon L, Massara F, Valeri Y, De Francesco L, Martino AM, Ghiglieno C, Schiavone M, Balla C, Dell’Era G, Pelargonio G, Forleo GB, Iacopino S, Sgarito G, Calo L, Tondo C, Dello Russo A, Patti G. Incidence of ventricular arrhythmias related to COVID infection and vaccination in patients with Brugada syndrome: Insights from a large Italian multicenter registry based on continuous rhythm monitoring. *J Cardiovasc Electrophysiol* 2023 May 17.
2. Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. *Circulation* 2022;105:73–78.
3. Gehi AK, Duong TD, Metz LD, Gomes JA, Mehta D. Risk stratification of individuals with the Brugada electrocardiogram: a meta-analysis. *J Cardiovasc Electrophysiol* 2006;17:577–583.
4. Letsas KP, Liu T, Shao Q, Korantzopoulos P, Giannopoulos G, Vlachos K, Georgopoulos S, Trikas A, Efremidis M, Deftereos S, Sideris A. Meta-analysis on risk stratification of asymptomatic individuals with the Brugada phenotype. *Am J Cardiol* 2015;116(1):98–103.
5. Sacher F, Probst V, Maury P, Babuty D, Mansourati J, Komatsu Y, Marquie C, Rosa A, Diallo A, Cassagneau R, Loizeau C, Martins R, Field ME, Derval N, Miyazaki S, Denis A, Nogami A, Ritter P, Gourraud B, Ploux S, Rollin A, Zemmoura A, Lamaison D, Bordachar P, Pierre B, Jais P, Pasquie JL, Hocini M, Legal F, Defaye P, Boveda S, Iesaka Y, Mabo P, Haissaguerre M. Outcome after implantation of a cardioverter defibrillator in patients with Brugada syndrome: a multicenter study-part 2. *Circulation* 2013;128:1739–1747.
6. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, Charron P, Corrado D, Dagues N, de Chillou C, Eckardt L, Friede T, Haugaa KH, Hocini M, Lambiase PD, Marijon E, Merino JL, Peichl P, Priori SG, Reichlin T, Schulz-Menger J, Sticherling C, Tzeis S, Verstrael A, Volterrani M; ESC Scientific Document Group. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022 Oct 21;43(40):3997-4126.
7. Sroubek J, Probst V, Mazzanti A, Delise P, Hevia JC, Ohkubo K, Zorzi A, Champagne J, Kostopoulou A, Yin X, Napolitano C, Milan DJ, Wilde A, Sacher F, Borggrefe M, Ellinor PT, Theodorakis G, Nault I, Corrado D, Watanabe I, Antzelevitch C, Allocca G, Priori SG, Lubitz SA. Programmed ventricular stimulation for risk stratification in the Brugada syndrome: a pooled analysis. *Circulation* 2016;133:622–630.