**Name of Journal:** *World Journal of Cardiology*

**Manuscript NO:** 41966

**Manuscript Type:** EDITORIAL

**Risk of sudden cardiac death: Are coronary chronic total occlusions an additional risk factor?**

Merinopoulos I *et al*. Chronic occlusions and SCD

Ioannis Merinopoulos, Natasha Corballis, Simon C Eccleshall, Vassilios S Vassiliou

**Ioannis Merinopoulos, Simon C Eccleshall, Vassilios S Vassiliou,** Department of Cardiology, Norfolk and Norwich University Hospital, Norwich NR4 7UY, United Kingdom

**Natasha Corballis,** Department of Cardiology, West Suffolk Hospital and University of East Anglia, Bury St Edmunds IP33 2QZ, United Kingdom

**Vassilios S Vassiliou,** Norwich Medical School, University of East Anglia, Norfolk and Norwich University Hospital, Royal Brompton Hospital and Imperial College London, Norwich NR4 7UQ, United Kingdom

**ORCID number:** Ioannis Merinopoulos (0000-0002-2059-0357); Natasha Corballis ([0000-0002-6837-5787](http://orcid.org/0000-0002-6837-5787)); Simon C Eccleshall ([0000-0002-6395-2389](http://orcid.org/0000-0002-6395-2389)); Vassilios S Vassiliou ([0000-0002-4005-7752](http://orcid.org/0000-0002-4005-7752)).

**Author contributions:** Merinopoulos I drafted the manuscript; Corballis N, Eccleshall SC and Vassiliou VS critically revised and approved the manuscript; Vassiliou VS conceived the idea.

**Conflict-of-interest statement:** The author declares no conflicts of interest regarding this paper.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Correspondence to: Vassilios S Vassiliou, FRCP (C), MA, MBBS, MRCP, PhD, Honorory Consultant Cardiologist,** Department of Cardiology,Norwich Medical School**,** Floor 2, Bob Champion Research and Education Building**,** James Watson Road, Norwich NR4 7UQ, United Kingdom. v.vassiliou@uea.ac.uk

**Telephone:** +44-16-03592534

**Fax:** +44-16-03592534

**Received:** September 13, 2018

**Peer-review started:** September 13, 2018

**First decision:** October 16, 2018

**Revised:** October 23, 2018

**Accepted:** November 15, 2018

**Article in press:**

**Published online:**

**Abstract**

Sudden arrhythmic cardiac death remains a significant, potentially reversible, cardiological challenge in terms of creating accurate risk prediction models. The current guidelines for implantable cardioverter defibrillator (ICD) therapy are mainly based on left ventricular ejection fraction despite its low sensitivity and specificity in predicting sudden cardiac death (SCD). Chronic total occlusions have been associated with increased mortality but further research is required to clarify if they should be incorporated in a risk model predicting SCD aiming to identify patients that would benefit from ICD therapy even with preserved ejection fraction.

**Key words:** Sudden cardiac death; Chronic total occlusion; Left ventricular ejection fraction; Implantable cardioverter defibrillator

**© The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip**: Further research is necessary in order to clarify if chronic total occlusion can be incorporated in a risk prediction model of sudden cardiac death aiming to identify patients that would benefit from implantable cardioverter defibrillator.

Merinopoulos I, Corballis N, Eccleshall SC, Vassiliou VS. Risk of sudden cardiac death: Are coronary chronic total occlusions an additional risk factor? *World J Cardiol* 2018; In press

**INTRODUCTION**

Even though death from cardiac causes has been decreasing over the last two decades in the western world, approximately 20% of all deaths and 50% of cardiovascular deaths are due to sudden cardiac death (SCD)[1,2]. Coronary chronic total occlusions (CTO) occur in about 16% of patients with significant ischaemic heart disease and they have been associated with increased mortality in a large prospective observational study[3]. However, currently it is not well known to what extent CTO increase SCD and if these patients would benefit from implantable cardioverter defibrillator (ICD) therapy.

In this Editorial, we focus on a recent article by Chi *et al*[4] published in JACC Clinical Electrophysiology as we feel it provides a new insight into the role of CTO in relation to prognosis and identifies gaps in knowledge that warrant further research. In this study the authors aimed to understand the relationship between CTO and the occurrence of ventricular tachycardia/fibrillation (VT/VF) or appropriate ICD therapy. They performed a meta-analysis including a total of 17 studies involving almost 55 thousand patients. They found that the presence of CTO was associated with higher risk of VT/VF or appropriate ICD therapy; however it was not associated with a difference in cardiac mortality or in all-cause mortality. The higher risk of VT/VF or appropriate ICD therapy was confirmed on both univariate and multivariate analysis (in only two studies), while the risk of cardiac mortality was significantly higher on univariate but not on multivariate analysis and the risk of all-cause mortality was not significantly higher in either univariate or multivariate analysis[4].

Comparing patients with infarct-related and non-infarct related CTOs, they concluded that the former had a higher risk of VT/VF or appropriate ICD therapy, cardiac mortality and higher all-cause mortality. The higher risk of VT/VF or appropriate ICD therapy of patients with infarct-related CTOs was confirmed on univariate but not multivariate analysis while the higher risk of cardiac mortality was only significant on multivariate analysis and the higher risk of all-cause mortality was significant on both univariate and multivariate analysis. Finally, non-revascularization of CTO was associated with higher risk of all-cause mortality but this did not reach statistical significance. The authors reached the conclusion that ICD implantation for primary or secondary prevention should be considered in patients who have infarct-related CTOs[4].

According to American Heart Association/American College of Cardiology/ Heart Rhythm Society (AHA/ACC/HRS) 2017, European Society of Cardiology (ESC) 2015 and United Kingdom National Institute for Health and Clinical Excellence (NICE) 2014 guidelines, an ICD is indicated for secondary prevention in survivors of cardiac arrest provided there is no reversible cause[5-7]. The decision for primary prevention ICD therapy varies slightly according to the various guidelines however, in general it depends on the left ventricular ejection fraction (LVEF), QRS duration and New York Heart Association (NYHA) class. The AHA/ACC/HRS 2017 guidelines recommend ICD if LVEF < 35% and NYHA II-III or LVEF < 30% and NYHA I. The ESC 2015 guidelines recommend ICD if LVEF < 35% and NYHA II-III[5]. According to NICE 2014 guidelines, primary prevention ICD therapy is indicated if LVEF < 35%, NYHA I-III and QRS duration > 120 ms. For patients who fulfil the first two criteria but QRS is < 120 ms, ICD is recommended if there is a high risk of SCD[7] and in this situation the current research[4] would perhaps suggest that presence of CTO can be a qualifying criterion for “high risk”[7].

Even though LVEF has a central role in the algorithm for recommending primary prevention ICD therapy, it has both low specificity and sensitivity for predicting SCD. It is established that low LVEF predicts not only SCD but also other modes of cardiovascular death as well[8]. In addition, only a minority of patients who suffer cardiac arrest will have LVEF < 35%. It is estimated that 40% of patients who suffer SCD have known heart disease with LVEF > 40%, while only 13% of patients who suffer SCD have known heart disease and LVEF < 40%[2]. It has also been shown that myocardial scar > 5% is an independent risk factor for all-cause mortality and appropriate ICD therapy, irrespective of LVEF[9]. In addition, looking at other pathologies for example dilated cardiomyopathy[10] and aortic stenosis[11], other parameters such as presence of myocardial fibrosis have been shown to have additional prognostic impact over and above LVEF.

**CONCLUSION**

Chi *et al*[4] have analysed 17 studies that had included patients with severely reduced LVEF but also patients with only mildly reduced or even normal LVEF. It remains to be seen whether CTO can be regarded as an independent factor for malignant arrhythmias over and above the information we get from LVEF, but this study certainly suggests that this should be investigated. In addition, further research can identify whether patients who have viable myocardium with evidence of reversible ischaemia in the presence of some myocardial scar in the CTO territory should also be considered for an ICD even after successful revascularisation. Even though we do not feel that definitive conclusions can be drawn from this analysis, it is an important study as it indicates that further research is needed in order to clarify the relationship of infarct-related CTO and non-infarct related CTO with SCD both in patients with reduced and preserved LVEF. It is well appreciated that the risk of SCD is continuous rather than dichotomous and no single parameter can adequately discriminate to dichotomise the risk[12]. Therefore, clarification if CTO is a high risk variable for SCD in patients with preserved LVEF (introducing a new term for such patients, the CTOpEF patients) or mid-range EF (CTOmrEF patients) or in patients with LVEF < 35% and narrow QRS would be very clinically relevant.

**REFERENCES**

1 **Sara JD**, Eleid MF, Gulati R, Holmes DR Jr. Sudden cardiac death from the perspective of coronary artery disease. *Mayo Clin Proc* 2014; **89**: 1685-1698 [PMID: 25440727 DOI: 10.1016/j.mayocp.2014.08.022]

2 **Wellens HJ**, Schwartz PJ, Lindemans FW, Buxton AE, Goldberger JJ, Hohnloser SH, Huikuri HV, Kääb S, La Rovere MT, Malik M, Myerburg RJ, Simoons ML, Swedberg K, Tijssen J, Voors AA, Wilde AA. Risk stratification for sudden cardiac death: current status and challenges for the future. *Eur Heart J* 2014; **35**: 1642-1651 [PMID: 24801071 DOI: 10.1093/eurheartj/ehu176]

3 **Råmunddal T**, Hoebers LP, Henriques JP, Dworeck C, Angerås O, Odenstedt J, Ioanes D, Olivecrona G, Harnek J, Jensen U, Aasa M, Albertsson P, Wedel H, Omerovic E. Prognostic Impact of Chronic Total Occlusions: A Report From SCAAR (Swedish Coronary Angiography and Angioplasty Registry). *JACC Cardiovasc Interv* 2016; **9**: 1535-1544 [PMID: 27491603 DOI: 10.1016/j.jcin.2016.04.031]

4 **Chi WK**, Gong M, Bazoukis G, Yan BP, Letsas KP, Liu T, Baranchuk A, Nombela-Franco L, Dong M, Tse G; International Health Informatics Study (IHIS) Network. Impact of Coronary Artery Chronic Total Occlusion on Arrhythmic and Mortality Outcomes: A Systematic Review and Meta-Analysis. *JACC Clin Electrophysiol* 2018; **4**: 1214-1223 [PMID: 30236396 DOI: 10.1016/j.jacep.2018.06.011]

5 **Priori SG**, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C, Van Veldhuisen DJ; ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015; **36**: 2793-2867 [PMID: 26320108 DOI: 10.1093/eurheartj/ehv316]

6 **Al-Khatib SM**, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Granger CB, Hammill SC, Hlatky MA, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RL. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. *Circulation* 2018; **138**: e272-e391 [PMID: 29084731 DOI: 10.1161/CIR.0000000000000549]

7 **Colquitt JL**, Mendes D, Clegg AJ, Harris P, Cooper K, Picot J, Bryant J. Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure: systematic review and economic evaluation. *Health Technol Assess* 2014; **18**: 1-560 [PMID: 25169727 DOI: 10.3310/hta18560]

8 **Albert CM**. Prediction of sudden cardiac death in patients with coronary heart disease: the challenge ahead. *Circ Cardiovasc Imaging* 2008; **1**: 175-177 [PMID: 19808539 DOI: 10.1161/CIRCIMAGING.108.825588]

9 **Klem I**, Weinsaft JW, Bahnson TD, Hegland D, Kim HW, Hayes B, Parker MA, Judd RM, Kim RJ. Assessment of myocardial scarring improves risk stratification in patients evaluated for cardiac defibrillator implantation. *J Am Coll Cardiol* 2012; **60**: 408-420 [PMID: 22835669 DOI: 10.1016/j.jacc.2012.02.070]

10 **Halliday BP**, Gulati A, Ali A, Guha K, Newsome S, Arzanauskaite M, Vassiliou VS, Lota A, Izgi C, Tayal U, Khalique Z, Stirrat C, Auger D, Pareek N, Ismail TF, Rosen SD, Vazir A, Alpendurada F, Gregson J, Frenneaux MP, Cowie MR, Cleland JGF, Cook SA, Pennell DJ, Prasad SK. Association Between Midwall Late Gadolinium Enhancement and Sudden Cardiac Death in Patients With Dilated Cardiomyopathy and Mild and Moderate Left Ventricular Systolic Dysfunction. *Circulation* 2017; **135**: 2106-2115 [PMID: 28351901 DOI: 10.1161/CIRCULATIONAHA.116.026910]

11 **Vassiliou VS**, Perperoglou A, Raphael CE, Joshi S, Malley T, Everett R, Halliday B, Pennell DJ, Dweck MR, Prasad SK. Midwall Fibrosis and 5-Year Outcome in Moderate and Severe Aortic Stenosis. *J Am Coll Cardiol* 2017; **69**: 1755-1756 [PMID: 28359524 DOI: 10.1016/j.jacc.2017.01.034]

12 **Deyell MW**, Krahn AD, Goldberger JJ. Sudden cardiac death risk stratification. *Circ Res* 2015; **116**: 1907-1918 [PMID: 26044247 DOI: 10.1161/CIRCRESAHA.116.304493]

**P-Reviewer:** Pastromas S, Ueda H, Maric I, Amrousy DE **S-Editor:** Dou Y **L-Editor: E-Editor:**

**Specialty type:** Cardiac and cardiovascular systems

**Country of origin:** United Kingdom

**Peer-review report classification**

Grade A (Excellent): A

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): E