# Correspondence

## Letter by Mareev et al Regarding Article, "Comparative Effectiveness of Implantable Cardioverter Defibrillators for Primary Prevention in Women"

Zeitler et al[1] suggest that implantable cardioverter defibrillators (ICDs) exert a similar reduction in mortality in men and women, but their estimate of the absolute reduction in mortality for either sex (≈7.5% at 1 year and 10% by 3 years) far exceeds that observed (about 0% and 5% at 1 and 3 years, respectively)[2] in randomized controlled trials (RCTs) These large differences require reconciliation.

RCTs could underestimate the impact of interventions in clinical practice. If true, this could have led to the rejection of many useful therapies. Selection criteria for inclusion in RCTs usually result in populations at intermediate risk; patients at low risk who have little to gain are excluded, as are those with complex or severe comorbidities, for fear that their outcome will be determined by problems that the intervention cannot modify. In RCTs of ICDs, patients in the ICD groups with few comorbidities had a 3-year mortality of ≈5%, rising to ≈20% in those with multiple comorbidities.[2] RCTs suggest that increasing age, comorbidity, and symptom severity attenuate the benefits of ICDs.[2–4] Zeitler et al[1] report a 3-year mortality ≈40% and suggest that the higher mortality might reflect greater age, comorbidity, or severity of heart failure in the observational cohort, none of which would account for a greater therapeutic effect of ICD in RCTs.

In RCTs, many patients do not receive their assigned intervention, diluting the observed benefit; ≈7% of patients assigned to an ICD either did not receive a device or had it explanted, whereas 5% to 11% of those assigned to the control group received an ICD. The control group in RCTs may be better managed and more likely to comply with advice than patients in routine clinical practice. Moreover, RCTs are fixed in time, but observational cohorts can be constantly updated. Accordingly, larger benefits in observational studies of ICDs may reflect improvements in technology and programming or poorer pharmacological management.

On the contrary, observational studies cannot reliably differentiate between the natural history of disease and the effects of intervention. Patients chosen for an intervention will differ from those who are not and it is uncertain whether any statistical adjustment can compensate for differences in observed and unobserved confounders. No contemporary cardiovascular therapy has been approved on the basis of an observational study.

Health economic analyses suggest that ICDs must exert a large effect on mortality to be a wise and cost-effective use of healthcare resources.[5] This either requires a large effect indeed for patients with a short life-expectancy because of problems other than sudden death or a cumulative benefit over decades among patients who are unlikely to die of anything other than arrhythmia.[4] We would welcome the authors' thoughts on this issue.

## Disclosures

Dr Mareev received ESC HFA research fellowship grant. C. Butcher received ISR Grant, Boston Scientific. Dr Cleland received research grants from Amgen, Novartis, Philips, and Servier; has served on advisory boards and speakers bureaus for Abbot, Amgen, Bayer, Medtronic, Philips, Servier, Stealth Biopharmaceuticals, and Vifor; and has served on the data and safety monitoring boards for Medtronic, Sorin, and Trevena.

**Yura Mareev, MD, PhD**
*Department of Cardiology*
*Imperial College*
*Royal Brompton and Harefield Trust*
*London, United Kingdom*

**Charles Butcher, MBBS, Bsc (Hons), MRCP**
*Department of Cardiology*
*Royal Brompton and Harefield Trust*
*London, United Kingdom*

**John G.F. Cleland, MD, PhD, FRCP, FESC, FACC**
*Department of Cardiology*
*Imperial College*
*Royal Brompton and Harefield Trust*
*London, United Kingdom*

## References

1. Zeitler EP, Hellkamp AS, Schulte PJ, Fonarow GC, Hernandez AF, Peterson ED, Sanders GD, Yancy CW, Al-Khatib SM. Comparative effectiveness of implantable cardioverter defibrillators for primary prevention in women. *Circ Heart Fail*. 2016;9:e002630. doi: 10.1161/CIRCHEARTFAILURE.115.002630.
2. Steinberg BA, Al-Khatib SM, Edwards R, Han J, Bardy GH, Bigger JT, Buxton AE, Moss AJ, Lee KL, Steinman R, Dorian P, Hallstrom A, Cappato R, Kadish AH, Kudenchuk PJ, Mark DB, Inoue LY, Sanders GD. Outcomes of implantable cardioverter-defibrillator use in patients with comorbidities: results from a combined analysis of 4 randomized clinical trials. *JACC Heart Fail*. 2014;2:623–629. doi: 10.1016/j.jchf.2014.06.007.
3. Hess PL, Al-Khatib SM, Han JY, Edwards R, Bardy GH, Bigger JT, Buxton A, Cappato R, Dorian P, Hallstrom A, Kadish AH, Kudenchuk PJ, Lee KL, Mark DB, Moss AJ, Steinman R, Inoue LY, Sanders G. Survival benefit of the primary prevention implantable cardioverter-defibrillator among older patients: does age matter? An analysis of pooled data from 5 clinical trials. *Circ Cardiovasc Qual Outcomes*. 2015;8:179–186. doi: 10.1161/CIRCOUTCOMES.114.001306.
4. Raphael CE, Finegold JA, Barron AJ, Whinnett ZI, Mayet J, Linde C, Cleland JG, Levy WC, Francis DP. The effect of duration of follow-up and presence of competing risk on lifespan-gain from implantable cardioverter defibrillator therapy: who benefits the most? *Eur Heart J*. 2015;36:1676–1688. doi: 10.1093/eurheartj/ehv102.
5. Sanders GD, Hlatky MA, Owens DK. Cost-effectiveness of implantable cardioverter-defibrillators. *N Engl J Med*. 2005;353:1471–1480. doi: 10.1056/NEJMsa051989.

**(*Circ Heart Fail*. 2016;9:72. DOI: 10.1161/CIRCHEARTFAILURE.116.003043.)**

Circulation
Heart Failure

American Heart Association®

# Letter by Mareev et al Regarding Article, ''Comparative Effectiveness of Implantable Cardioverter Defibrillators for Primary Prevention in Women''

Yura Mareev, Charles Butcher and John G.F. Cleland

*Circ Heart Fail.* 2016;9:
doi: 10.1161/CIRCHEARTFAILURE.116.003043
*Circulation: Heart Failure* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3289. Online ISSN: 1941-3297