This is the accepted version of a letter to the editor, published in Circulation. (Morris, Moxon and Gollege, Circulation 2015 131(21):e508).

Letter by Morris et al regarding article "Improved quality of life after 1 year with an invasive versus a noninvasive treatment strategy in claudicants: One-year results of the Invasive Revascularization or Not in Intermittent Claudication (IRONIC) Trial"

Dylan R. Morris[1], Joseph V. Moxon[1], Jonathan Golledge[1,2]

1. The Vascular Biology Unit, Queensland Research Centre for Peripheral Vascular Disease, School of Medicine and Dentistry, James Cook University, Townsville Australia.

2. Department of Vascular and Endovascular Surgery, The Townsville Hospital, Townsville Australia.

Address for Correspondence:

Professor Jonathan Golledge

Queensland Research Centre for Peripheral Vascular Disease

School of Medicine and Dentistry

James Cook University

Queensland, Australia 4811

jonathan.golledge@jcu.edu.au

Tel: + 61 7 4781 4730

Fax: + 61 7 4781 5945

Journal Subject Codes: Cardiovascular (CV) surgery:[39] CV surgery: other, Treatment:[27] Other treatment.

This is the accepted version of a letter to the editor, published in Circulation. (Morris, Moxon and Gollege, Circulation 2015 131(21):e508).

To the Editor:

We congratulate Nordanstig and colleagues on the Invasive Revascularization Or Not in Intermittent Claudication (IRONIC) trial, which investigated the potential benefit of lower extremity revascularisation in patients with stable intermittent claudication (IC).[1] This trial reported that revascularisation improves quality of life in selected IC patients. Despite the substantial achievement of completing this trial, we feel that some caution is required in the interpretation of the results.

First, as the authors point out, the control group did not receive supervised exercise therapy as this is not widely available in Europe. Supervised exercise therapy has been shown to provide symptom reduction similar to lower extremity revascularisation, and may have additional benefits in terms of cardiovascular risk reduction.[2] The additional value of revascularisation over supervised exercise alone is controversial. Previous small trials have reported no quality of life benefit from revascularisation and exercise therapy compared to exercise therapy alone although they may have been underpowered to examine this comparison.[3,4]

Second, the IRONIC trial did not examine the impact of revascularisation on day-to-day physical activity which may be assessed using devices such as accelerometers. Greater day-to-day physical activity in patients receiving invasive treatment in comparison with conservative management would suggest the potential for additional benefit in terms of cardiovascular risk reduction, supporting the use of revascularisation.

Finally, additional data may facilitate interpretation of the findings of the IRONIC trial. The authors report that patients with bilateral symptoms were included in the current study. However the number of patients with bilateral symptoms, and their distribution between treatment groups is not reported. Bilateral IC is common and has implications in achieving

beneficial results through revascularisation in our opinion. Furthermore, the authors did not provide details of the number of patients receiving angiotensin converting enzyme inhibitors such as Ramipril which have recently been reported to improve IC symptoms.[5] Thus the influence of these drugs on the assessed outcome measures is unclear. It is also unclear why so many patients remained on cilostazol after revascularisation. Finally, the event-free survival was lower in the intervention group (77% vs 88%). We presume that this difference was not significant but the trend is concerning. Larger studies and longer follow-up are needed to be sure that interventional approaches to IC do not put patients at greater event rate risk and to assess the durability of this form of treatment.

We commend Nordanstig and colleagues for their endeavours to improve the management of IC. It is hoped that ongoing work in this area will lead to improvements in both quality of life and cardiovascular risk reduction in IC patients.

Funding Sources

JG holds a Practitioner Fellowship from the National Health and Medical Research Council, Australia (1019921) and a Senior Clinical Research Fellowship from the Office of Health and Medical Research. The funding bodies had no role in the construction of this paper.

Disclosures

None.

References

1. Nordanstig J, Taft C, Hensater M, Perlander A, Osterberg K, Jivegard L. Improved quality of life after 1 year with an invasive versus a non-invasive treatment strategy in

claudicants: one-year results of the Invasive Revascularization or Not in Intermittent Claudication (IRONIC) Trial. *Circulation.* 2014; 130:939-947.

2. Bermingham SL, Sparrow K, Mullis R, Fox M, Shearman C, Bradbury A, Michaels J. The cost-effectiveness of supervised exercise for the treatment of intermittent claudication. *European Journal of Vascular and Endovascular Surgery*. 2013; 46:707-714.
3. Greenhalgh RM, Belch JJ, Brown LC, Gaines PA, Gao L, Reise JA, Thompson SG, Mimic Trial Participants. The adjuvant benefit of angioplasty in patients with mild to moderate intermittent claudication (MIMIC) managed by supervised exercise, smoking cessation advice and best medical therapy: results from two randomised trials for stenotic femoropopliteal and aortoiliac arterial disease. *European Journal of Vascular and Endovascular Surgery*. 2008; 36:680-688.
4. Mazari FA, Khan JA, Carradice D, Samuel N, Abdul Rahman MN, Gulati S, Lee HL, Mehta TA, McCollum PT, Chetter IC. Randomized clinical trial of percutaneous transluminal angioplasty, supervised exercise and combined treatment for intermittent claudication due to femoropopliteal arterial disease. *British Journal of Surgery.* 2012; 99:39-48.
5. Ahimastos AA, Walker PJ, Askew C, Leicht A, Pappas E, Blombery P, Reid CM, Golledge J, Kingwell BA. Effect of ramipril on walking times and quality of life among patients with peripheral artery disease and intermittent claudication: a randomized controlled trial. J*ournal of the American Medical Association.* 2013; 309:453-460.