Applying randomised trials to the real world: A VOYAGER of discovery

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Running head:

Applying randomised trials to the real world

Category:

Commentary

Word count:

494

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The choice of antithrombotic therapy for patients undergoing intervention for peripheral arterial diseases is complex, with different antithrombotics appearing to be the best option for different patient groups.[1] The COMPASS and VOYAGER trials aimed to simplify these decisions.[2,3] While COMPASS examined patients with stable peripheral arterial disease, VOYAGER examined patients undergoing intervention. The headline findings were similar in that 'dual pathway inhibition' with aspirin and low dose rivaroxaban reduced the primary endpoint (a composite of limb and cardiovascular events), at the cost of increased major bleeding events.[2,3] The trials were intended to be pragmatic, with broad inclusion criteria so that antithrombotic prescribing could be simplified to a single treatment strategy.

Unfortunately, as highlighted by two recent papers published in the *Journal*, the exclusion criteria were also broad and excluded many 'real world' patients, often due to perceived bleeding risk. Lapébie et al. reported on the external applicability of both COMPASS and VOYAGER to patients in the French COPART registry, finding that only 30.1% of patients would have been eligible for inclusion in either trial.[4] In this issue of the *Journal*, Søgaard et al. present a similar analysis of patients in the Danish Vascular Registry, finding 27.1% of patients would have been eligible.[5]

Both studies found that patients in the registries (both eligible and ineligible for the trials) were at higher risk of major ischaemic events than those in the control arms of the trials, making it conceivable that dual pathway inhibition might be even more beneficial than the results of the trials would suggest. The study by Søgaard et al. adds a note of caution: rates of major bleeding were also substantially higher among Danish registry patients.

These real-world findings are not surprising, and highlight reasons why antithrombotic choices seem so confusing, even with so many RCTs.[1] Essentially, patients at higher risk of major ischaemic events (for example the subgroup with chronic limb-threatening ischaemia), who would benefit the most from 'better' antithrombotics, will also have more bleeding events on the treatment, and are consequently underrepresented in trials. Trial subgroup analysis and 'real world'

application of trial results shine a harsh spotlight on these issues.[4,5] The all-important risk balance is then debated extensively by clinicians trying to do the right thing for an individual patient.

So how can this be improved in the future? Firstly, we must ensure that patients who may benefit the most from treatment are properly represented in randomised controlled trials. The second is to better quantify the balance between ischaemic and bleeding events: preventing an amputation is not the same as causing a nosebleed from which the patient is hospitalised but quickly recovers. Finding where this balance lies requires trialists to engage with patients to discover what matters most to them and is a major driver for the development of Core Outcome Sets.[6] Until we understand what patients value most from their treatment, and design trials to address these outcomes, we will struggle to translate the results of randomised trials to the individual 'real world' patient.

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