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Published in:
European Heart Journal

DOI:
[10.1093/eurheartj/eh403](https://doi.org/10.1093/eurheartj/eh403)

Publication date:
2019

Document Version
Publisher's PDF, also known as Version of record

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):
Rutherford, E., & Struthers, A. D. (2019). Pentaerythrityl tetranitrate (PETN): a better nitrate? *European Heart Journal*, 40(46), e23-e25. <https://doi.org/10.1093/eurheartj/eh403>

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Pentaerythrityl tetranitrate (PETN): a better nitrate?

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This Editorial refers to ‘Efficacy of the long acting nitro vasodilator pentaerythrityltetranitrate in patients with chronic stable angina pectoris receiving antianginal background therapy with betablockers: a 12-weeks, randomized, double-blind, placebo controlled trial’, by Münzel et al. doi:10.1093/eurheartj/eh403. The paper was inadvertently published in Volume 35, Issue 14 without this editorial.

Today, patients with coronary artery disease can expect to live longer and with less symptom burden than their counterparts of 30 years ago. This is because of better medical therapies and better revascularization strategies. However, the stalwarts of medical anti-anginal therapy—the b-blockers, calcium channel blockers, and nitrates—are not without their problems. Nitrates, although effective at relieving acute anginal pain and well established as a mainstay of chronic angina therapy, may have particular problems.^{1,2} One problem with nitrates is that traditional nitrate use can increase oxidative stress and so induce endothelial dysfunction.¹ In addition to endothelial dysfunction, another major practical problem with nitrate is nitrate tolerance.² Furthermore, a review of 52 693 patients from the Global Registry of Acute Coronary Evidence shows that longer-term use of nitrates is associated with fewer ST elevation myocardial infarctions but more non-ST elevation acute coronary syndromes.³ One hypothesis is that nitrates might pre-condition the heart more towards ischaemic episodes. Newer medical therapies—or new applications of existing therapies—are therefore needed to reduce the symptom burden in chronic stable angina and, if possible, to improve prognosis. This need is particularly relevant to those who have run out of revascularization options.

This is the approach taken by Münzel et al. in the featured paper.⁴ They take a fresh look at the long-acting organic nitrate pentaerythrityl tetranitrate (PETN), which has been used as an anti-anginal medication for over half a century (Figure 1).⁵ In this work, they chose to investigate the anti-ischaemic effect of PETN for two reasons. Firstly, as they and others have previously described, it does not appear to exhibit the same tolerance-inducing properties as other nitrates.^{2,6} Secondly, unlike other nitrates, which are reputed to induce endothelial dysfunction, there is evidence that in animal models PETN even improves endothelial function.^{7,8} This has been

partly attributed to the ancillary property of PETN of inducing the antioxidant enzyme haem oxygenase.⁷ It is probable that the lack of induction tolerance of tolerance by PETN and its suggested beneficial effects on endothelial function are interlinked. In mice, when the haem oxygenase gene was knocked out, both tolerance and progressive endothelial dysfunction were evident after exposure to PETN.⁸ Disappointingly, however, despite evidence to the contrary in animal models, when the PENTA study examined the effect of PETN on endothelial function in patients with coronary artery disease, no improvement in endothelial function was demonstrated, although positive changes in the microcirculation were seen.⁹

It may not be coincidence that other therapies thought to have positive effects on endothelial function have also been demonstrated to have anti-anginal or anti-ischaemic properties.^{10–12} In other words, the idea that improving endothelial function and reducing oxidative stress can reduce ischaemia in chronic stable angina is not new. Testosterone¹² and allopurinol¹¹ are two drugs to do this. Both have been demonstrated to improve endothelial function and have shown encouraging results in the treatment of the pain of angina.^{10–12} The role of testosterone as an anti-anginal therapy is impractical, however, in view of its significant side-effect profile. In contrast, allopurinol is well established as a safe drug that is cheap, well tolerated and has few side-effects. The anti-anginal efficacy of allopurinol awaits further evaluation in larger-scale and longer-term clinical trials.

In the multinational study by Münzel et al.,⁴ the authors sought to investigate the anti-ischaemic efficacy of PETN 80 mg twice daily over placebo in patients with chronic stable angina who were already on standard anti-anginal therapy including a b-blocker and/or ivabradine. The primary outcome was total exercise duration at 12 weeks. After a wash-out period from any other long-acting nitrates, patients underwent treadmill testing at randomization, 6 and 12 weeks. Ultimately, in the unselected patient group PETN fared no better than placebo. This is both disappointing and surprising, because a systematic review and meta-analysis of randomized clinical trials considering nitrate therapy in stable angina found that both intermittent and continuous regimens of nitrates lengthened exercise duration significantly by 31 and 53 s, respectively.¹³ However, PETN, which is a pentaerythrityl nitrate, was not included in the review search terms; it had already been removed from the pharmacopoeia in North America and Europe by the early 1990s because of a lack of data supporting its efficacy.

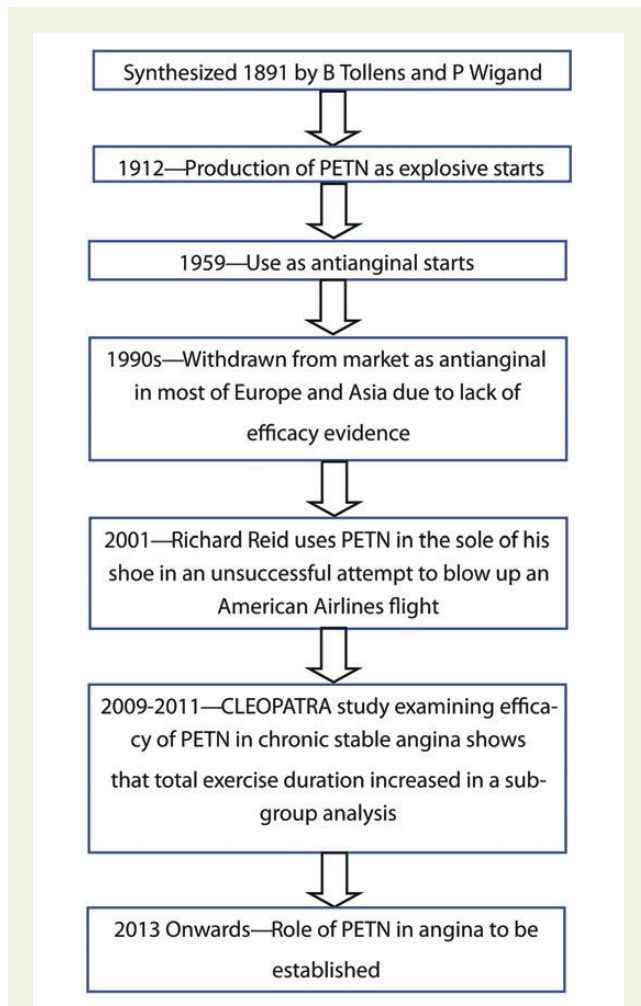


Figure 1 The history of PETN. Adapted from information in Münzel et al.^{1,4} and *Encyclopedia Britannica* (<http://www.britannica.com/EBchecked/topic/454067/PETN>).

Münzel's featured study did, however, have some significant positive findings in a subgroup analysis of those participants who were most symptomatic with their angina.⁴ In 120 patients who reported two episodes or more of angina per week, who took at least two doses of short-acting nitrates per week, and who exercised for less than 9 min at baseline, the change in total exercise duration was markedly larger in the PETN group when compared with placebo. In fact, the changes in total exercise duration were quite dramatic, with the change from baseline reaching as much as 48 s in favour of the PETN group; this is comparable with the data from the systematic review of traditional nitrate therapy.¹³ It is perhaps to be expected that the efficacy of PETN would be greater in those with the worst symptoms.

Ranolazine, which is a relatively new second-line anti-anginal, has also been studied in severe angina. The CARISA study¹⁴ included patients with known stable angina who were on conventional anti-anginal therapy with standard doses of atenolol, amlodipine, or diltiazem. The study eligibility criteria included a limited total exercise capacity on treadmill testing (3–9 min of a modified Bruce protocol). Patients were randomized to receive either placebo or two differing doses of ranolazine. Total exercise duration was again a primary

outcome measure. Ranolazine therapy only extended trough exercise duration by close to 24 s.¹⁴ However, in a subsequent *post hoc* analysis of 258 patients from the CARISA trial who were considered to be on maximally tolerated doses of β -blockers or calcium-channel blockers (determined by assessment of blood pressure and heart rate), ranolazine extended the change in baseline exercise duration to 34.5 s.¹⁵ Ivabradine, another accepted second-line anti-anginal in Europe, also achieved fairly modest improvements in total exercise time (16.6 s longer than placebo) when compared with the results of PETN.¹⁶ The increase in exercise duration in the subgroup analysis of the PETN data is comparable with a similar, albeit smaller, study of allopurinol in unselected angina patients. In that study, the absolute improvement in exercise duration over placebo was 58 s.¹¹ We must consider all of these relatively modest improvements in exercise duration before we discount the potential efficacy of PETN. However, before we can definitively establish whether PETN can really hold its own amongst other anti-anginal drugs, direct comparative studies are required.

Given the acceptable safety profile and demonstrated clinical benefits of PETN in a carefully selected patient population, as well as its reported lack of some traditional nitrate therapy drawbacks, there is likely to be a place for its use amongst other emerging anti-anginal therapies. However, further evidence of its merit is still required. The natural next question for PETN proponents is surely whether PETN therapy could modify longer-term outcomes in the ischaemic heart disease population. Indeed, this is the test we need now to apply to all our new anti-ischaemic treatments in chronic stable angina.

Conflict of interest: A.D.S. and the University of Dundee have a patent for the use of xanthine oxidase inhibitors to treat angina pectoris. No other conflicts of interest are declared.

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