

# Antiplatelet treatment for acute secondary prevention of non-cardioembolic minor stroke / transient ischaemic attack: an update for the acute physician

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## ABSTRACT

Acute stroke is the leading cause of disability in the UK and a leading cause of mortality worldwide. The majority of patients with ischaemic stroke present with minor deficits or transient ischaemic attack (TIA), and are often first seen by patient-facing clinicians. Urgent evaluation and treatment are important as many patients are at high risk of major vascular events and death within hours to days after the index event. This narrative review summarises the evidence on four antiplatelet treatments for non-cardioembolic stroke prevention: aspirin, clopidogrel, dipyridamole and ticagrelor. Each of these drugs has a unique mechanism and has been tested as a single agent or in combination. Aspirin, when given early is beneficial and short-term treatment with aspirin and clopidogrel has been shown to be more effective in high-risk TIA / minor stroke. This review concludes by highlighting gaps in evidence, including scope for future trials that could potentially change clinical practice.

**KEYWORDS:** antiplatelets, stroke prevention, stroke risk, recurrent stroke, transient ischaemic attack

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## Introduction

Acute stroke affects more than 100,000 adults in the UK each year and is a leading cause of death and severe disability.<sup>1</sup> About two-thirds of patients present with a minor stroke and ~20% have a history of transient ischaemic attack (TIA) in the hours to days preceding the event.<sup>2</sup> Most TIAs and minor strokes are caused by thromboembolic occlusion of the cerebral arteries (artery-to-artery embolism) and early treatment with antiplatelet agents reduce the risk of recurrent stroke by about two-thirds.<sup>3,4</sup>

The majority of patients with suspected TIA and minor stroke are first assessed by patient-facing clinicians, so we begin by highlighting the common scores used to guide triage decisions, predict stroke recurrence and prognosticate on the basis of clinical information and brain imaging. We summarise the latest evidence for two established antiplatelets (aspirin and clopidogrel) for acute treatment either as single agents or combined, citing major trials, systematic reviews and meta-analyses in minor stroke and TIA. In addition, we appraise the effect of dipyridamole along with aspirin and the emerging role of ticagrelor, highlighting gaps in evidence and future clinical trials.

## Risk of recurrent stroke

The risk of a recurrent stroke within 3 months of a minor stroke or TIA is high (~10%–20%) with the majority occurring within days of the index event.<sup>5</sup> Multiple risk scores have been developed to predict early stroke. The commonly used are ABCD, ABCD2 and, more recently, ABCD3 consisting of age, blood pressure, clinical symptoms of TIA, presence of diabetes mellitus, dual TIA (two or more TIAs within 7 days) and duration of symptoms.<sup>6,7</sup> Recently, a new score has been developed (namely ABCD3-I) that includes abnormal findings on brain and carotid artery imaging (ie presence of ipsilateral significant carotid stenosis or acute diffusion-weighted hyperintensity (DWI) on magnetic resonance imaging (MRI)), and is shown to predict the risk of recurrent stroke better than those including clinical components alone (Table 1).<sup>1,7</sup> Another study has suggested adding perfusion scanning to ABCD3-I to improve risk prediction in secondary care settings.<sup>8</sup>

**Table 1. Risk scores to predict severity of transient ischaemic attack and stroke recurrence**

	ABCD2 score	ABCD3 score	ABCD3-I score
<b>Characteristic</b>			
Age ≥60 years	1	1	1
Blood pressure ≥140/90 mmHg	1	1	1
<b>Clinical features</b>			
Unilateral weakness	2	2	2
Speech disturbance without weakness	1	1	1
Duration of symptoms:			
<10 minutes	0	0	0
10–59 minutes	1	1	1
≥60 minutes	2	2	2
Diabetes mellitus	1	1	1
Dual TIA (2nd TIA in ≤7 days)	-	2	2
<b>Imaging</b>			
Acute diffusion-weighted hyperintensity on imaging	-	-	2
Ipsilateral ≥50% stenosis of internal carotid artery and/or major cerebral artery	-	-	2
<b>Patients at high risk, total score</b>	6–7	6–9	8–13 <sup>a</sup>
<b>Risk of stroke in high-risk patients, day 7, %</b>	11	9	14
<b>Risk of stroke in high-risk patients, day 90, %</b>	12	12	15

<sup>a</sup>To be validated prospectively. TIA = transient ischaemic attack.

One limitation of these scores is that they do not predict stroke risk based on potential aetiology (eg extracranial or intracranial carotid stenosis, cardioembolism and small vessel disease). Moreover, these scores may not be useful in:

- > young patients, with no vascular risk factors
- > cases of TIA in the posterior circulation
- > patients with amyloid angiopathy who have transient focal neurological events (termed 'amyloid spells'), which probably indicate haemorrhage (especially superficial cortical siderosis or focal subarachnoid haemorrhage) rather than ischaemia.

Establishing a definite diagnosis of TIA can be difficult and it is important to highlight that none of the aforementioned risk prediction scores are substitutes for clinical assessment, appropriate investigations or changes to treatment. In the UK, guidelines recommend that patients with suspected TIA should be seen within 24 hours, regardless of their risk score.<sup>9</sup>

## Aspirin

Of all antiplatelet agents, aspirin is the most widely researched, inexpensive, readily available and routinely prescribed treatment for acute ischaemic stroke and TIA.<sup>10–12</sup> In two mega trials (>40,000 patients), treatment with aspirin within 48 hours of symptom onset and continued for 2–4 weeks resulted in a 23% overall odds reduction of vascular events and similar reduction in non-fatal strokes.<sup>13</sup>

Another analysis assessing the time course effects showed that aspirin reduced the 6-week risk of recurrent ischaemic stroke by ~60% and disabling or fatal ischaemic stroke by approximately 70% with the greatest benefit within 48 hours of treatment.<sup>14</sup> Importantly, the effects were independent of age, gender and aetiology of TIA or stroke.<sup>14</sup>

One common clinical question is whether it is safe to give aspirin without a brain scan to exclude intracranial haemorrhage. Haemorrhage is rare in patients with symptoms of TIA and accounts for less than 5% of minor strokes.<sup>15</sup> Moreover, studies suggest that even if aspirin is started and intracranial haemorrhage is subsequently diagnosed, such patients do not clinically deteriorate.<sup>9,10</sup> Taking into account the potential benefits versus risks, the National Institute for Health and Care Excellence (NICE) guidelines advise that patients with suspected TIA should receive a loading dose of aspirin 300 mg (without prior imaging) and be referred urgently to a specialist clinic.<sup>9</sup>

## Clopidogrel

In a subgroup analysis of the large Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, 6,431 patients with recent ischaemic stroke (mean time from stroke onset to randomisation was 53 days) were randomised to clopidogrel 75 mg once daily or aspirin 325 mg once daily.<sup>16</sup> At 2 years, clopidogrel did not significantly reduce the risk of recurrent stroke (risk reduction (RR) 7.3%; *p*=0.28) compared with aspirin but did reduce risk in patients with peripheral arterial disease (RR 23.8%; *p*=0.0028).<sup>16</sup> Importantly, there were fewer gastrointestinal and intracranial haemorrhages associated with clopidogrel.<sup>16</sup>

## Dipyridamole

To-date, five trials have tested the combination of aspirin with dipyridamole.<sup>17</sup> Of these, one trial included patients with TIA and the others also included minor stroke.<sup>17</sup> The majority of data (~80%) come from two trials: the European Stroke Prevention Study 2 (ESPS-2) trial and the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT).<sup>18,19</sup> In these two trials, comparisons were between aspirin plus dipyridamole versus aspirin, while the other three trials compared treatment with placebo or dipyridamole alone.<sup>20</sup> A meta-analysis combining these trials included 7,612 patients and examined 1,158 outcomes (composite of vascular death, non-fatal stroke and myocardial infarction).<sup>17</sup> The results showed that the combination of aspirin plus dipyridamole was more effective in preventing recurrent stroke than aspirin (hazard ratio (HR) 0.78; 95% confidence interval (CI) 0.68–0.90) independent of age, sex, index event and risk factors.<sup>17</sup> A pooled analysis examining the mechanism of action found that the addition of dipyridamole to aspirin had no effect on the risk or severity of early recurrent ischaemic stroke in

the first 12 weeks of the index TIA / minor stroke but significantly reduced the risk of disabling or fatal stroke thereafter.<sup>14</sup>

### Aspirin plus clopidogrel in minor stroke and TIA

The Fast Assessment of Stroke and Transient ischaemic attack to prevent Early Recurrence (FASTER) trial was the first trial to test the combination of aspirin plus clopidogrel compared with aspirin alone within 24 hours of minor stroke and TIA.<sup>21</sup> In this trial, patients in the combined treatment arm had fewer recurrent strokes but more haemorrhages at 90-day follow-up.<sup>21</sup>

With this insight, two trials tested the efficacy and safety of clopidogrel and aspirin in preventing recurrent stroke in patients with minor ischaemic stroke (National Institutes of Health Stroke Scale  $\leq 3$ ) or high-risk TIA (ABCD2  $\geq 4$ ).<sup>22,23</sup> In the larger trial, the Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial, 5,170 patients were randomised within 24 hours of onset and for the first 21 days to either clopidogrel (300 mg loading dose followed by 75 mg daily) and aspirin (75–300 mg loading dose followed by 75 mg daily) or aspirin alone (75–300 mg loading dose followed by 75 mg daily).<sup>22</sup> At day 90, there was a significant difference in recurrent stroke reduction at day 90 in the clopidogrel plus aspirin group compared with aspirin alone (8.2% vs. 11.7%, respectively; HR 0.68;  $p < 0.001$ ).<sup>22</sup> Moreover, there were fewer events in the composite endpoint of stroke, myocardial infarction and cardiovascular death in the dual treatment group without a significant increase in bleeding.<sup>22</sup> A secondary analysis showed that the benefits of treatment were sustained at 1 year.<sup>24</sup>

It should be noted that the CHANCE trial was conducted in China, so the results may not be generalised to Europe or North America. Moreover, one-half of the patients did not receive statins and two-thirds were not treated with antihypertensive drugs raising the issue of adequate risk-factor management.<sup>22</sup>

By comparison, the Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT) trial randomised patients within 12 hours and treatment with aspirin (50–325 mg daily) plus clopidogrel (loading dose of 600 mg, followed by 75 mg daily) was continued for 90 days.<sup>23</sup> The results for the reduction in recurrent ischaemic stroke were similar to the CHANCE trial with the greatest benefit observed between day 7 to day 30.<sup>23</sup> However, there were significantly more haemorrhages in the clopidogrel plus aspirin group than aspirin alone group, largely due to non-fatal intracranial haemorrhage (HR 2.45; 95% CI 1.01–5.90).<sup>23</sup> The conclusion from the results of the two trials is that for every 1,000 patients treated with aspirin plus clopidogrel, treatment would prevent 15 ischaemic strokes and cause five major haemorrhages.<sup>22,23</sup>

It is noteworthy that in the CHANCE trial, clopidogrel plus aspirin compared with aspirin alone reduced the risk of a new stroke only in the subgroup of patients who were non-carriers of the cytochrome P450 2C19 (*CYP2C19*) enzyme gene. *CYP2C19* is a critical enzyme in the conversion of clopidogrel to its active metabolite and a number of polymorphisms have been shown to decrease the metabolism.<sup>25</sup> However, these results were not replicated in the POINT trial and potential explanations include the smaller sample size in the tested subgroup, lower number of gene carriers of *CYP2C19*, higher loading dose of clopidogrel, smaller sample size and less tobacco use, which is known to affect the metabolism of clopidogrel.<sup>26</sup>

The clinical implication of the CHANCE and POINT trials is that the combination of clopidogrel plus aspirin within hours of index minor stroke / TIA and continued for 21 days is effective in reducing recurrent stroke and major vascular events and outweigh the risks of bleeding.<sup>26</sup> Another trial, the Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS) trial showed similar effects within 12 to 24 hours of treatment but did not show overall benefit.<sup>27</sup> Moreover, there was an increased risk of bleeding in the group randomised to three antiplatelets (aspirin, clopidogrel and dipyridamole) compared with patients treated with either clopidogrel or aspirin plus dipyridamole for 30 days.<sup>27</sup>

It is important to highlight that the longer-term treatment trials examining the efficacy of clopidogrel and aspirin in patients with acute ischaemic stroke or TIA suggest a lack of benefit and probable harm. In this context, three large trials should be mentioned. The first was the Management of AtheroThrombosis with Clopidogrel in High-risk patients (MATCH) trial, a randomised, double-blind, placebo-controlled trial comparing clopidogrel (75 mg once daily) plus aspirin (75 mg once daily) versus clopidogrel alone in 7,599 patients with TIA and stroke, and the larger Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial enrolled nearly twice as many patients with established cardiovascular disease or multiple risk factors.<sup>28,29</sup> In the MATCH trial, there was no significant benefit for aspirin and clopidogrel versus clopidogrel alone in the primary outcome of composite vascular events (15.7% vs 16.7%, respectively;  $p = 0.24$ ) and recurrent stroke (10.6% vs 11.3%, respectively;  $p = 0.32$ ). Importantly, life-threatening haemorrhages were more frequent with clopidogrel plus aspirin than clopidogrel alone (2.6% vs 1.3%, respectively), as was major bleeding (2% vs 1%, respectively).<sup>28</sup> Similar results were reported with clopidogrel plus aspirin in the CHARISMA trial at the end of the 28-month follow-up period.<sup>29</sup>

The third is the Secondary Prevention of Small Subcortical Strokes (SPS3) trial, which was the first stroke prevention trial in a well-defined population of lacunar infarcts.<sup>30</sup> In this trial, 3,020 patients were randomised to receive 75 mg clopidogrel or placebo, in addition to 325 mg aspirin. The trial was stopped early due to more adverse event rates among patients assigned to combination treatment.<sup>31</sup> There was no difference in the risk of recurrent stroke between the groups (HR 0.92; 95% CI 0.72–1.16) and higher mortality in the clopidogrel plus aspirin group compared with aspirin (HR 1.52; 95% CI 1.14–2.04;  $p = 0.004$ ).

In the setting of carotid surgery in patients with acute ischaemic stroke or TIA, the benefit versus risks of aspirin and aspirin combined with clopidogrel have been assessed. One analysis showed that either aspirin or aspirin combined with clopidogrel was associated with a reduced risk of peri-procedural death or ischaemic stroke.<sup>32</sup> Another large study (28,683 patients) showed that the combination of aspirin and clopidogrel was associated with a 40% risk reduction of neurological events but patients were more likely to have bleeding requiring surgical exploration.<sup>33</sup> These results along with other data suggest that aspirin alone or combined with clopidogrel could be useful in carotid surgery but the dose and duration of treatment need further exploration.<sup>34</sup>

### Aspirin plus dipyridamole versus clopidogrel

The Prevention Regimen For Effectively avoiding Second Strokes (PROFESS) trial was designed after a network meta-analysis

including >42,000 TIA or stroke patients with 6,830 vascular events suggested that aspirin plus dipyridamole might be more effective than clopidogrel or aspirin alone.<sup>35</sup>

To-date, the PRoFESS trial is the largest stroke trial to investigate the prevention of recurrent stroke and included 20,332 participants. The median time to enrolment from the index ischaemic stroke was 15 days, with 40% of patients randomised within 10 days.<sup>35</sup> The trial was initially designed to compare 25 mg aspirin plus extended-release dipyridamole 200 mg against clopidogrel 75 mg daily and aspirin, but the protocol was amended to clopidogrel alone after 2,027 patients were recruited. At 2.5 years, aspirin plus dipyridamole and clopidogrel alone showed broadly similar efficacy in preventing recurrent strokes and vascular events, but there were more intracranial haemorrhages in patients treated with aspirin plus dipyridamole compared with clopidogrel alone (4.1% vs 3.6%, respectively).<sup>35</sup> There was no difference between the groups on disability and cognitive decline.<sup>36</sup>

### Ticagrelor

Unlike clopidogrel, ticagrelor does not require conversion from the prodrug to the active form in the liver. As a result, it has faster onset of action and is known to have a more potent platelet inhibitor effect. Ticagrelor is reversible and short acting so must be given twice daily. The Acute Stroke Or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial directly compared the effects of ticagrelor (180 mg loading dose then 90 mg twice daily) versus aspirin in 13,199 patients with minor stroke or high-risk TIA.<sup>37</sup> There was a trend towards benefit with ticagrelor in preventing recurrent ischaemic stroke (5.8% vs 6.7%, respectively;  $p=0.046$ ) and major vascular events (6.7% vs 7.5%, respectively) compared with aspirin.<sup>37</sup> There were no differences in major bleeding, intracranial haemorrhage or fatal bleeding.

### Ticagrelor plus aspirin in minor stroke and TIA

The combination of ticagrelor plus aspirin versus aspirin alone was tested in the large Acute Stroke or Transient Ischaemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death (THALES) trial where patients with mild to moderate stroke (National Institutes of Health Stroke Scale  $\leq 5$ ) or high-risk TIA (ABCD2 score  $\geq 6$ ) within 24 hours of symptom onset were recruited.<sup>38</sup> Patients were treated for 30 days. The primary outcome of recurrent stroke or death occurred in 303 patients in the ticagrelor plus aspirin group compared with 362 patients in the aspirin alone group (HR 0.83; 95% CI 0.71–0.96;  $p=0.02$ ); this difference was driven by participants in the ticagrelor plus aspirin group having fewer ischaemic strokes ( $n=276$ ) than those randomised to aspirin ( $n=345$ ).<sup>38</sup> Conversely, major bleeding was higher in the ticagrelor plus aspirin group compared with the aspirin alone group (0.5% vs 0.1%, respectively;  $p=0.001$ ).<sup>38</sup>

### Ticagrelor in addition to aspirin in minor stroke and TIA?

Data from the recent trials raise the interesting question of whether clinicians can now choose ticagrelor instead of clopidogrel in addition to aspirin for minor stroke and TIA. There is some evidence that aspirin plus ticagrelor could be effective based on

the results of one trial in acute coronary syndrome but there are no head-to-head comparisons after stroke or TIA.<sup>39</sup> The risk reduction and number needed to treat in the POINT and CHANCE trials with aspirin plus clopidogrel compared with aspirin alone are more favourable than those for aspirin plus ticagrelor compared with aspirin alone in the THALES. However, eligibility criteria for these trials differ so direct comparison is not appropriate. Similarly, there was a lower reported risk of intracranial haemorrhage with aspirin plus clopidogrel compared with aspirin plus ticagrelor. While this is similar to findings in a trial following acute coronary syndrome, direct comparison again would not be appropriate.<sup>40</sup> Importantly, it should be highlighted that the dose of aspirin was higher in THALES (300–325 mg) than in the trials of clopidogrel plus aspirin (75–162.5 mg).<sup>38</sup> Extrapolating these results to patients with cerebrovascular disease who are likely to be older with fragile vascular beds is probably not appropriate.<sup>40</sup>

Recently, the CHANCE-2 trial assessed the effects of ticagrelor plus aspirin versus clopidogrel plus aspirin in Chinese *CYP2C19* loss-of-function carrier patients after minor stroke or TIA.<sup>41</sup> At 90 days, there were fewer strokes in the ticagrelor group (6.0%) compared with the clopidogrel group (6.0% vs 7.6%, respectively; HR 0.77; 95% CI 0.64–0.94).<sup>41</sup> There was no difference in major bleeding between the two groups but ticagrelor was associated with more bleeding than clopidogrel.

Taking into account the aforementioned results, a head-to-head comparison trial testing aspirin plus clopidogrel versus aspirin plus ticagrelor in a UK population with or without genetic testing seems warranted.

### Recurrent stroke on antiplatelets

One-third to one-half of patients who have a recurrent stroke are already taking antiplatelet therapy.<sup>42</sup>

Some patients are 'resistant' to aspirin (~3%) or clopidogrel (~28%–44%) and causes include non-adherence, inadequate dosing, interactions with drugs (such as proton pump inhibitors), genetic polymorphisms of the cyclo-oxygenase enzyme or *P2Y12*, other genes involved in thromboxane biosynthesis, upregulation of non-platelet sources of thromboxane biosynthesis, and increased platelet turnover.<sup>42,43</sup> It is difficult to determine the reasons for treatment resistance as non-compliance is an issue, particularly among the elderly.<sup>43</sup> At present, there is little evidence for routinely testing patients for antiplatelet resistance in ischaemic stroke / TIA and, apart from encouraging compliance, clinicians usually switch between single agents or use a combination of aspirin and clopidogrel, or use adjusting formulations. It is unclear whether these measures are more effective, safe or cost effective, so well-designed clinical trials in this area are urgently needed.

### Clinical guidelines

In 2019, NICE updated the guidelines for secondary prevention of non-cardioembolic stroke or TIA.<sup>9</sup> It stated that standard treatment would be clopidogrel 75 mg daily for ischaemic stroke and off-label in TIA. The guideline also stated that aspirin 75 mg daily with modified-release dipyridamole 200 mg twice daily may be used if clopidogrel cannot be tolerated.<sup>9</sup> If both clopidogrel and aspirin cannot be tolerated or contra-indicated, modified-release dipyridamole 200 mg twice daily may be used. Based on the results of the CHANCE and POINT trials, international guidelines recommend aspirin and clopidogrel for 3 weeks, but highlight that

the benefit of treatment is limited if not started early (<7 days) after the index event.<sup>44–46</sup>

### Conclusion and future directions

There is strong evidence for aspirin initiation in acute ischaemic stroke or TIA and, to date, no other single antiplatelet agent has been shown to be superior in the acute setting.

Regarding combination therapy, the data suggest benefit for clopidogrel plus aspirin in preventing early recurrent events, if treatment is started early and given in the short term. The aforementioned results suggest a potential role for ticagrelor in the acute minor stroke / TIA population but more research is needed.<sup>45</sup>

Further trials are also needed on:

- > which antiplatelet treatment or combination is effective in the long term, its timing and duration
- > the efficacy and safety among specific subgroups of patients according to clinical characteristics, and laboratory or genetic tests
- > the benefit of switching antiplatelet agents for patients who are already taking one medication at the time of stroke/TIA.

For the clinician suspecting TIA, aspirin should be prescribed immediately unless contra-indicated. Too many patients are being discharged without this simple, inexpensive treatment (£1.26 per pack of 28 tablets) that substantially reduces the risk and severity of early recurrent stroke.<sup>14</sup>

### Key points

- > Patients with ischaemic stroke or TIA are at a substantially high risk of a major stroke and a large proportion of these occur within hours to the first few days of the index event.
- > It is essential that a loading dose of aspirin 300 mg is given to patients with suspected TIA or minor stroke immediately (with or without prior brain imaging). Minor stroke or ongoing symptoms need urgent referral to the hyper-acute stroke unit.
- > Recent trials suggest that early initiation of low-dose aspirin plus clopidogrel for 3 weeks further reduces recurrent stroke and major vascular events without significantly increasing the risk of bleeding. Guidelines advocate this approach, but clinicians should carefully assess these benefits when managing patients. ■

### Supplementary material

Additional supplementary material may be found in the online version of this article at [www.rcpjournals.org/clinmedicine](http://www.rcpjournals.org/clinmedicine): S1 – A comparison of antiplatelet dose, half-life and side effects, and a summary of key clinical trials and meta-analyses of antiplatelets in TIA and acute and subacute/chronic stroke.

### Conflicts of interest

Kailash Krishnan is a recipient of a research fellowship awarded by the division of medicine at Nottingham University Hospitals NHS Trust. Philip M Bath is Stroke Association professor of stroke medicine, chief investigator of the TARDIS trial and has consulted for Sanofi. Nikola Sprigg was the deputy chief investigator of the TARDIS trial. Jatinder S Minhas is an NIHR clinical lecturer in older people and complex health needs. Timothy J England is CRN

East Midlands speciality lead for stroke. Thompson G Robinson is an NIHR senior investigator and the national speciality lead for stroke for the NIHR Clinical Research Network. Jesse Dawson is the clinical lead Scottish Stroke Research Network / NRS Stroke Research champion. Jason P Appleton is supported, in part, by an NIHR Health and Care Research Scholarship.

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