An evaluation of the effect of an angiotensin-converting enzyme inhibitor on the growth rate of small abdominal aortic aneurysms: a randomized placebo-controlled trial (AARDVARK)

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Aims

The AARDVARK (Aortic Aneurysmal Regression of Dilation: Value of ACE-Inhibition on RisK) trial investigated whether ACE-inhibition reduces small abdominal aortic aneurysms (AAA) growth rate, independent of blood pressure (BP) lowering.

Methods and results

A three-arm, multi-centre, single-blind, and randomized controlled trial (ISRCTN51383267) was conducted in 14 hospitals in England. Subjects aged ≥55 years with AAA diameter 3.0–5.4 cm were randomized 1:1:1 to receive perindopril arginine 10 mg, or amlodipine 5 mg, or placebo and followed 3–6 monthly over 2 years. The primary outcome was aneurysm growth rate (based on external antero-posterior ultrasound measurements in the longitudinal plane), determined by multi-level modelling to provide maximum likelihood estimates. Two hundred and twenty-four subjects were randomized (2011–2013) to placebo (n = 79), perindopril (n = 73), or amlodipine (n = 72). Mean (SD) changes in mid-trial systolic BP (12 months) were 0.5 (14.3) mmHg, P = 0.78 compared with baseline, −9.5 (13.1) mmHg (P < 0.001), and −6.7 (12.0) mmHg (P < 0.001), respectively. No significant differences in the modelled annual growth rates were apparent [1.68 mm (SE 0.2), 1.77 mm (0.2), and 1.81 mm (0.2), respectively]. The estimated difference in annual growth between the perindopril and placebo groups was 0.08 mm (CI 0.50, 0.65). Similar numbers of AAAs in each group reached 5.5 cm diameter and/or underwent elective surgery: 11 receiving placebo, 10 perindopril, and 11 amlodipine.

Conclusion

Small AAA growth rates were lower than anticipated, but there was no significant impact of perindopril compared with placebo or placebo and amlodipine, combined despite more effective BP lowering.

Keywords

Abdominal aortic aneurysm • ACE-inhibition • Perindopril • Blood pressure lowering • Calcium channel blocker • Placebo-controlled

Introduction

Each year in England and Wales ~4000 deaths are attributed to abdominal aortic aneurysm (AAA) rupture. There is a high mortality associated with rupture (70–80%) and a much smaller but significant mortality from elective aneurysm repair (1.3–4.7%). However, four randomized trials have shown that for small, slow growing asymptomatic AAAs between 3.0 and 5.4 cm in diameter surveillance is safe. Therefore, patients with small AAAs are generally enrolled on a surveillance programme, with repair considered once the AAA diameter reaches 5.5 cm in size. After the compelling results of the aneurysm screening trials, the National Health...
Service Abdominal Aortic Aneurysm Screening Programme (NAAASP) was introduced in 2009 in the UK, with similar programmes in Sweden and elsewhere. Consequently, many smaller AAAs are now being detected early. The majority (80%) of screen-detected AAAs are small, with diameters of 3.0–4.4 cm. If AAA growth rates can be attenuated or halted in this expanding cohort of patients, there is an opportunity to reduce the number of patients at risk of AAA repair and rupture.

Animal studies have suggested a potential role of the renin–angiotensin system (RAS) in AAA formation and growth. A case–control study on a group of over 15,000 patients with an AAA, reported that patients who had previously received an angiotensin-converting enzyme inhibitor (ACE-I) but not other antihypertensive agents were 20% less likely to present with ruptured aneurysm. Similarly, the Chichester small AAA surveillance study suggested an association between angiotensin receptor blocker (ARB) prescription and reduced AAA progression. Conversely, post hoc analysis from both the UK Small Aneurysm Trial and the PHAST trial failed to show that ACE-I slow aneurysm growth. Given the, albeit inconsistent, observational evidence that RAS-blockade might restrict AAA progression or lead to a decrease in the risk of rupture, the AARDVARK (Aortic Aneurysmal Regression of Dilation: Value of ACE-Inhibition on RisK) trial was designed.

The primary objective of this trial was to investigate whether an ACE-I, perindopril, would reduce the growth rate of small AAAs compared with placebo, independent of blood pressure (BP) reduction, assessed by including a third comparator arm in which BP was lowered by amlodipine.

Methods

The study was approved by the Fulham Research Ethical Committee (NRES 10/H0711/80) and was registered with the International Standard Randomized Controlled Trial Number registry (ISRCTN51383267). The full protocol is available on the NIHR HTA website.

Study design

This study was a randomized, single-blind, multicentre, and placebo-controlled trial. Patients were randomized into one of three parallel arms, receiving placebo, or perindopril (10 mg arginine salt), or amlodipine (5 mg) daily. The doses of perindopril and amlodipine were estimated to have similar effects on BP thereby allowing an evaluation of whether any benefits of perindopril on AAA growth observed were independent of BP reduction.

Trial participants

Men or women, aged at least 55 years, with AAA 3.0–5.4 cm in diameter by internal (inner anterior wall to the inner posterior (ITI) wall), or intima to intima) or external (from the outer anterior to the outer posterior (OTO) wall or adventitia to adventitia) measurement according to ultrasonography and a systolic BP < 150 mmHg who consented to participation in the trial were recruited. Patients were excluded if they were already required to take an ACE-I, ARB, or a calcium channel blocker – with the exception of 5 mg amlodipine, had known renal artery stenosis (>50%), had a serum creatinine of > 180 μmol/L, were unable to give informed consent, were too frail to travel for 3–6 monthly surveillance, were reported to have any clinically significant medical condition (including reduced life expectancy of <2 years), were unable or unwilling to comply with study requirements, were participating in another trial of a product or device within the previous 30 days, or had a known intolerance to perindopril or amlodipine.

Recruitment

Participants were recruited from 14 sites across England and six patient identification centers that referred potential participants to the associated research site for trial recruitment.

The clinical registers and the NAAASP databases at sites were used to identify patients with small AAA. These patients were then pre-screened against trial inclusion and exclusion criteria and given participant information. Reasons for ineligibility or non-participation were recorded.

Trial eligibility was assessed at screening visits at which demographic information, past medical history, and current medication history was recorded. The most recent AAA ultrasound measurements were reviewed and written informed consent was obtained. Thereafter BP recordings and blood samples for creatinine and electrolytes were taken.

Where the systolic BP of patients was >150 mmHg at screening, and s/he was otherwise eligible for inclusion in the trial, sites were asked to arrange for the patient to receive indapamide SR 1.5 mg daily or amlodipine 5 mg, if the patient was not already taking a calcium channel blocker. Their BP measurements were repeated after 6 weeks and if the systolic BP fell to <150 mmHg, patients were eligible to proceed to randomization. For recruited patients who were not receiving a statin, sites requested the patients’ General Practitioner to prescribe one as per current guidelines.

Randomization and masking

Randomization was carried out through a web-based system using a 1:1:1 ratio among the three randomized groups, stratified by centre and into one of two ranges of baseline aneurysm size: 3.0–4.5 and 4.51–5.40 cm. Randomization codes were generated using randomly permuted blocks of varying sizes (Stata Corporation, TX, USA) by an independent statistician. The trial was classified as single blind since the three tablets prescribed were not identical in appearance. Drugs were dispensed in identical opaque bottles and while technically patients could have investigated the composition of their prescribed trial drug, neither patients, ultrasonographers nor site investigators were aware of which tablets had been prescribed to each patient.

Drugs were debulked into bottles labelled A, B, or C and dispensed at each visit. For the initial 2 weeks following randomization, patients were asked to take half doses of their trial drug, in line with standard clinical practice for the initiation of perindopril, and therefore applied to all three randomized groups.

Where in-trial cough was persistent and intolerable, patients stopped the trial drug for 2 weeks and if the cough resolved they were changed to losartan (100 mg/day). If the cough continued and hence deemed unrelated to trial drug, the drug was restarted. All patients who were switched to losartan continued in the trial and were followed up on an intention to treat basis.

Compliance with the trial drug was evaluated using tablet counts by a designated member of the pharmacist. Compliance (expressed as a percentage) was calculated as a ratio of tablets taken (based on pill counts of tablets returned) divided by the number of tablets that should have been consumed.

Trial procedures

Each patient had a maximum of nine planned study visits. At the baseline visit, patients underwent a review of informed consent, demographic information, medical history, and current medical therapies. In addition,
ACE inhibition and aneurysm growth

The full CONSORT diagram is shown in Figure 1. In all, 10 patients withdrew from the study or died before completing at least two study visits—an attrition rate of 4%. The mean duration of follow-up of the placebo, perindopril, and amlopidine groups was 617, 623, and 584 days, respectively.

Throughout the trial, mean systolic and diastolic BP levels remained largely unchanged among those allocated to placebo but fell in the amlopidine group, and more so in the perindopril group (Figure 2). For example, mean changes in systolic BP midway through the trial (12 months) were 0.5 mmHg (standard deviation 14.3, }
Table 1  Baseline characteristics of randomized patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Perindopril</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>79</td>
<td>73</td>
<td>72</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70.7 (7.5)</td>
<td>71.6 (6.9)</td>
<td>71.5 (6.7)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>74 (94%)</td>
<td>71 (97%)</td>
<td>66 (92%)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>79 (100%)</td>
<td>73 (100%)</td>
<td>71 (99%)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>131.7 (12.2)</td>
<td>130.9 (11.5)</td>
<td>131.9 (13.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77.9 (7.6)</td>
<td>76.7 (8.0)</td>
<td>78.0 (7.0)</td>
</tr>
<tr>
<td>Use of statins, n (%)</td>
<td>48 (61%)</td>
<td>53 (73%)</td>
<td>45 (63%)</td>
</tr>
<tr>
<td>AAA external diameter longitudinal (cm)</td>
<td>4.06 (0.67)</td>
<td>4.05 (0.65)</td>
<td>4.03 (0.69)</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>17 (22%)</td>
<td>21 (29%)</td>
<td>18 (25%)</td>
</tr>
<tr>
<td>Pack years for current smokers</td>
<td>32.9 (28.0)</td>
<td>33.1 (24.0)</td>
<td>29.3 (17.3)</td>
</tr>
<tr>
<td>Past smokers, n (%)</td>
<td>56 (72%)</td>
<td>41 (57%)</td>
<td>44 (63%)</td>
</tr>
<tr>
<td>Pack years past smokers</td>
<td>42.2 (45.5)</td>
<td>42 (33.8)</td>
<td>40.5 (36.8)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.4 (8.5)</td>
<td>175.9 (8.3)</td>
<td>173.7 (8.7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.3 (16.1)</td>
<td>84.3 (16.6)</td>
<td>81.2 (13.8)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>8 (10.1%)</td>
<td>2 (2.7%)</td>
<td>6 (8.3%)</td>
</tr>
<tr>
<td>Anti-platelet therapy, n (%)</td>
<td>28 (35.4%)</td>
<td>37 (50.6%)</td>
<td>33 (45.8%)</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless otherwise stated.

0.78 compared with baseline), $-9.5 \text{ mmHg (13.1, } P < 0.001)$, and $-6.7 \text{ mmHg (12.0, } P < 0.001)$ in the placebo, perindopril, and amlodipine groups, respectively. Mean changes in diastolic BP at 12 months were $-0.2 \text{ mmHg (standard deviation 7.3, } P = 0.78$ compared with baseline), $-5.8 \text{ mmHg (8.1, } P < 0.001)$, and $-4.7 \text{ mmHg (7.5, } P < 0.001)$. 

Figure 1  AARDVARK CONSORT diagram.
The estimated average annual AAA diameter growth was 1.68 mm (standard error 0.2) in the placebo group, 1.77 mm (0.2) in the perindopril group, and 1.81 mm (0.2) in the amlodipine group (Table 2). The differences in the average growth rates were not significant between perindopril and placebo ($P = 0.78$). The estimated difference in annual growth between the perindopril and placebo groups was 0.08 mm (confidence intervals $-0.50$, $0.65$). The difference in average growth rate between those allocated to perindopril and amlodipine groups was not significant ($P = 0.89$) nor was the difference between those allocated to perindopril, compared with those allocated to placebo and amlodipine combined ($P = 0.92$). Maximum likelihood estimates for longitudinal external AAA diameter growth adjusted for baseline age–sex, statin use, and current smoking status showed very similar results. A sensitivity analysis, excluding the few patients with diabetes, did not affect the overall finding with an estimated difference in annual growth rate between the perindopril and placebo groups of $-0.01$ mm with 95% confidence intervals of $-0.6$, $0.6$ mm. A further sensitivity analysis, including the three post-randomization exclusions, also showed no difference in annual growth rate between any of the groups. Also including the site in the model as random effect or fixed effect did not change the results.

No significant differences were found among the three randomized groups (11, 10, and 11 in the placebo, perindopril, and amlodipine groups, respectively) in terms of the number of patients who reached the composite secondary endpoint of time taken to reach 5.5 cm or being referred to/having surgery or AAA rupture (Figure 3). There were no AAA ruptures.

Mean compliance combining all three groups was 81–88% for each 3-month period evaluated. There was no significant difference in compliance between groups at any time point.

Both active drugs were generally well tolerated with similar numbers of patients discontinuing therapy for AEs among the three groups (8, 13, and 14 among those randomized to the placebo, perindopril, and amlodipine groups, respectively). Six patients withdrew from the trial due to AEs attributed to study medications (two attributed to perindopril, four to amlodipine). Four patients (three randomized to perindopril and one to amlodipine) switched to losartan due to cough.

Small differences in the numbers of SAEs were reported among the three trial groups (16, 19, and 12 events in the placebo, perindopril, and amlodipine groups, respectively) but none of the recorded SAEs were deemed to be related to the trial medications by the principal investigators at the sites where the events occurred. There were non-significant minor differences in the median serum creatinine concentration recorded at each stage of the trial in those allocated to placebo and amlodipine. However, a 6% non-significant increase in serum creatinine was apparent at 3 months in those allocated to perindopril and similarly elevated levels were maintained thereafter. No patients were withdrawn from the trial due to concerns about renal function.
Table 2  Maximum likelihood estimates from linear mixed model for (a) longitudinal external abdominal aortic aneurysms diameter growth (mm) and (b) mean abdominal aortic aneurysms diameter estimates (mm) at 24 months

<table>
<thead>
<tr>
<th>Fixed parameters</th>
<th>Estimate</th>
<th>Standard error</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td></td>
<td></td>
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<tr>
<td>Average baseline diameter for the control group</td>
<td>40.74</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Average growth rate (mm/year) for the control group</td>
<td>1.68</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Difference in average baseline diameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perindopril vs. placebo</td>
<td>−0.08</td>
<td>1.06</td>
<td>0.94</td>
</tr>
<tr>
<td>Amlodipine vs. placebo</td>
<td>−0.21</td>
<td>1.06</td>
<td>0.85</td>
</tr>
<tr>
<td>Difference in average growth rate (mm/year):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perindopril vs. Placebo</td>
<td>0.08</td>
<td>0.29</td>
<td>0.78</td>
</tr>
<tr>
<td>Amlodipine vs. Placebo</td>
<td>0.12</td>
<td>0.30</td>
<td>0.68</td>
</tr>
<tr>
<td>Test for overall three group growth rate difference*</td>
<td></td>
<td></td>
<td>0.91</td>
</tr>
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</table>

| Random parameters                      |          |                |       |
| SD of individual intercepts           | 6.46     | 0.31           |       |
| SD of individual slopes               | 1.49     | 0.11           |       |
| Correlation between intercepts and slopes | 4.55    | 0.75           |       |
| SD of residual errors                 | 1.36     | 0.03           |       |

<table>
<thead>
<tr>
<th>Treatment</th>
<th>24 month estimate</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>44.11</td>
<td>[42.26, 45.96]</td>
</tr>
<tr>
<td>Perindopril</td>
<td>44.19</td>
<td>[42.25, 46.13]</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>44.15</td>
<td>[42.20, 46.10]</td>
</tr>
</tbody>
</table>

*For treatment by time interaction ($\chi^2$ test (2 d.f.)).

Figure 3  Kaplan–Meier estimates of proportion of patients reaching 5.5 cm in abdominal aortic aneurysms diameter during the course of the trial or having/being referred for abdominal aortic aneurysms surgery. Ten randomized patients are not included since they were only seen at baseline. One further patient was not included in the Kaplan–Meier graph as at baseline had one of the four diameter measurements ≥5.5. There is an apparent disparity with numbers of patients attending their 24-month visit largely due to this visit occurring before 720 days.
Discussion

In this randomized trial the ACE-I, perindopril did not affect the overall growth rate of small AAAs during 2 years of follow-up compared with amlodipine or placebo. The estimated difference in annual growth rate between perindopril and placebo remained similar after adjustment for known factors that affect aneurysm growth rate and after sensitivity analysis excluding patients with diabetes which is associated with reduced AAA growth rate. Additionally, in this trial there was no difference in the number of trial patients whose AAA grew to a maximum diameter of 5.5 cm or more and/or were referred for or received elective repair. The AARDVARK trial was designed, to study AAA growth, as a pilot trial for a larger trial of the impact of ACE-Is on AAA-related adverse clinical events including rupture and surgical repair.

Mean BP levels in the perindopril and amlodipine arms showed significant reductions between baseline and 24 months, but there were no differences in growth rates between those in the placebo group and those in the two actively treated groups. Although there is a known association between raised BP and aneurysm prevalence (particularly high diastolic readings),21 evidence to support increased aneurysm growth rates in hypertensive patients is lacking. This trial suggests that at least among those with baseline systolic BP <150 mmHg, a systolic/diastolic BP reduction using perindopril, compared with placebo, of on average ~8/5 mmHg throughout the trial (Figure 2A and B) does not have a significant impact on AAA growth rate.

This trial was designed to evaluate any BP independent effect in AAA growth rate of perindopril. Hence, the doses of perindopril and amlodipine were selected to achieve similar reductions in BP. Therefore, any BP-independent effects of ACE-I on AAA growth rates could be evaluated. However, although both treatments were effective in lowering BP, there were surprisingly greater reductions in systolic and diastolic BP in those receiving perindopril despite similar withdrawal and compliance rates in each group. This greater reduction in BP by an ACE-I in an elderly population of patients with AAA deserves further study. One possible explanation could be that patients had a high rate of unrecognized renal artery stenosis and ACE-Is are particularly effective in terms of BP lowering in this context.

The overall findings of the AARDVARK trial are at odds with several laboratory and animal-based studies9–11 including the findings that angiotensinogen and the angiotensin type 1 receptors (but not angiotensin type 2 receptors) are increased by a factor of 2 in the walls of AAAs compared with control tissue.11 Similarly in hypercholesterolaemic mice, infusion of angiotensin II leads to dissection of the aorta, generating supra-renal aortic aneurysms, the formation of which can be prevented with use of an ACE-I.9 In addition, perindopril has also been shown to inhibit aortic degeneration and AAA formation in other AAA animal models induced by elastase and calcium chloride.10 Similarly, some11 but not all14,15 large observational studies have generated findings which are inconsistent with these AARDVARK trial findings, in suggesting that RAS-blockade may protect against the growth of AAAs. It is not clear why these inconsistencies arise but may at least in part be related to confounding due to the reduced use of ACE-Is by smokers in the observational analyses.

The AAA growth rates observed in this trial were smaller than reported in previous studies6,7,22–24 where growth rates ranged between 1.6 and 2.6 mm per year in aneurysms with a mean baseline diameter between 3.4 and 4.3 cm. This may be secondary to the more aggressive control of cardiovascular risk factors, which is more routinely found in current clinical practice than was the case at the time of these previous studies and to the pre-requisite of a reasonably ‘controlled’ baseline systolic BP level before entry to the AARDVARK trial. The average baseline BPs in studies that have primarily measured small AAA growth rate were certainly higher than those of the participants in the AARDVARK trial (131.5/77.5 mmHg at baseline) ranging from 143 to 157 mmHg (systolic) and 81–91 mmHg (diastolic).5,7,22,23 Limitations of the AARDVARK trial include the potential for being under-powered to detect a small but important effect on AAA growth rate. Sample size calculations were based on an estimated annual growth rate in AAA diameter of 2.6 mm (SD 1.8) and a treatment effect of 38% (1 mm) as reported in the UKSAT trial.6 Given the actual average growth rate observed of 1.7 mm with an SD of 3.0, 190 patients per group would have been required to detect a 1 mm difference in annual growth with a power of 90%. Given the sample size (75 per group) this trial had 51% power to detect a 1 mm difference in growth (between two groups) and 85% power to detect a difference of 1.5 mm (close to the annual growth rate). However, the estimated difference in annual growth between the perindopril and placebo groups was 0.08 mm with confidence intervals of −0.50, 0.65. This statistically excludes a likely reduction of 1 mm per year with perindopril administration. The potential for lack of generalizability of the results must be acknowledged, since this trial was performed in a largely white male population, whose BP levels were relatively well controlled. In addition, the results may not be applicable to patients with larger aneurysms, but since 80% of screen-detected aneurysms have diameters of 3.0–4.4 cm1 it appears unlikely that ACE-I would slow the growth of most screen-detected aneurysms. Finally, there is a possibility that there may be an effect of ACE-I administration that is only evident after 2 years.

Despite these limitations, this is a unique randomized controlled trial investigating the effect of ACE-I on small aneurysm growth rates followed up for 2 years. Although a small and expected increase in creatinine levels was seen in the ACE-I group, trial withdrawals due to study drug-related AEs were similar among the three groups and compliance with therapy was excellent in all three treatment arms.

In conclusion, the AARDVARK trial, which is the first randomized trial to report the effect of ACE-Is in this setting, found no evidence that in patients with systolic BP of <150 mmHg, the rate of growth of small AAAs is slowed by the administration of the ACE-I perindopril compared with placebo and that modest BP lowering did not beneficially impact on the growth of small AAAs. Consequently, although perindopril was well tolerated and safe in a population of patients with AAA, the growing number of patients with small aneurysms found as a result of increased monitoring and screening appear unlikely to benefit from ACE-I administration in terms of the growth of their small AAAs.

Authors’ contributions

C.B. contributed to the design of the study, recruitment, interpretation of the trial findings, and prepared the first draft of this manuscript with G.K. G.K. was the trial manager and contributed to the design of the study, the management and delivery of the trial, interpretation of the results and prepared the first draft of this
manuscript with C.B. E.F. was responsible for the interim and final statistical analysis of the study, contributed to the design of the study and the writing of the manuscript. J.P. contributed to the design of the study, recruitment, interpretation of the trial findings, and the writing of this manuscript. N.P. contributed to the design of the study, recruitment, interpretation of the trial findings, to the writing of this manuscript and held overall oversight and responsibility for the study. E.F. performed statistical analysis. Trial management committee: C.B., G.K., E.F., J.P., N.P., trial steering committee, and data monitoring committee, handled funding and supervision. Investigational site collaborators acquired the data. Grant applicants conceived and designed the research. C.B., G.K. drafted the manuscript. C.B., G.K., E.F., J.P., N.P. made critical revision of the manuscript for key intellectual content.

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References


