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Antihypertensive drugs for secondary prevention after ischemic stroke or TIA: a systematic review and meta-analysis

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ABSTRACT

Background and Purpose. Approximately 30% of ischemic strokes occur after a previous stroke or TIA. Arterial hypertension is one of the best established risk-factors for first and recurrent stroke, both ischemic and hemorrhagic. Guidelines for the secondary prevention of ischemic stroke support the use of blood pressure-lowering drugs in most patients. However, the evidence for these recommendations comes from meta-analyses that included both ischemic and hemorrhagic stroke patients, whereas these two conditions differ quantitatively in several aspects. With this systematic review and meta-analysis, we aimed at summarizing the current evidence on blood pressure-lowering drugs for secondary prevention in patients with ischemic stroke or TIA.

Methods. We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials up to January 31st 2020. We included randomized controlled trials (RCTs) comparing any specific blood pressure-lowering drug, as monotherapy or combination, with either a control or another blood pressure-lowering drug.

Results. Eight studies that enrolled 33,774 patients with ischemic stroke or TIA were included in the meta-analysis. Mean follow-up was 25 months (range 3-48). Moderate-quality evidence indicated that a subsequent stroke occurred in 7.9% (ischemic in 7.4% or hemorrhagic in 0.6%) of patients taking any type of blood pressure-lowering drug compared with 9.7% of patients taking placebo (Odds Ratio (OR), 0.79 [95% Confidence Interval (CI), 0.66 to 0.94]; Absolute Risk Difference (ARD), -1.9% [95% CI, -3.1 to -0.5%]). Moderate-quality evidence indicated that mortality occurred similarly in patients taking any type of blood pressure-lowering treatment compared with placebo, with an absolute risk of 7.3% and 7.9% respectively (OR, 1.01 [95% CI, 0.92 to 1.10]; ARD, 0.1% [95% CI, -0.6 to 0.7%]).

Conclusions. The use of blood pressure-lowering drugs in patients with ischemic stroke or TIA is associated with a 1.9% risk reduction of stroke but does not affect the all-cause mortality risk.

Non-standard Abbreviations and Acronyms: BP: blood pressure; RCTs: randomized controlled trials; TIA: transient ischemic attack.

INTRODUCTION

Stroke is the second most common cause of death worldwide and it is expected to remain one of the leading causes of death and adult disability for the foreseeable future. Annually, 15 million people have a stroke, of which one third will die and one third will be permanently disabled.[1-3] Although primary prevention is most important in reduction of the burden of stroke, effective secondary prevention is also essential. About 85% of strokes are ischemic, the remaining are hemorrhagic. Approximately 30% of ischemic strokes occur in individuals with a previous stroke or transient ischemic attack (TIA), which are also at higher risk for subsequent myocardial infarction and death from vascular causes; recurrent ischemic strokes are more severe than first strokes.[4,5]

Arterial hypertension is one of the best established risk-factors for first and recurrent stroke, both ischemic and hemorrhagic.[2,6] Evidences from meta-analyses of randomized controlled trials (RCTs), most of which were conducted across all stroke types, support the use of blood pressure (BP)-lowering drugs for reducing the risk of recurrent stroke.[7-11] However, given the heterogeneous causes and hemodynamic consequences of ischemic and hemorrhagic strokes, the management of BP in adults with stroke is complex and additional high-quality evidence concerning antihypertensive use for secondary prevention by index stroke type is needed.[6,12]

With this systematic review and meta-analysis, we aimed at summarizing the current evidence on BP-lowering drugs for secondary prevention in patients qualifying with with ischemic stroke or TIA and at estimating the relative efficacy and safety of various drug classes.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Protocol and registration

The systematic review protocol was developed using guidance from the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) statement.[13] We addressed all 17 items within the PRISMA-P checklist, and registered the review in PROSPERO (CRD42018100148).[14] The manuscript was written accordingly to the PRISMA statement.[15]

Search strategy and selection criteria

We conducted a systematic review and meta-analysis. We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases from inception date to January 31st 2020, with no language restrictions. Search terms included extensive controlled vocabulary (MeSH and EMTREE) and keywords, including the names of antihypertensive drugs along with differing terms for stroke and cerebrovascular disease in various combinations (Supplemental Material). Reference lists of relevant RCTs or review were also handsearched. Details on the search strategies can be found on PROSPERO protocol.[14] We did not formally search for additional unpublished or ongoing studies because, from a preliminary check on ClinicalTrials.gov (http://www.clinicaltrial.gov/) and International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/), we did not identify additional studies relevant for the review question.

Eligibility criteria and study selection

We included RCTs comparing any BP-lowering drug, as monotherapy or combination therapy, with either a control (placebo or no therapy) or another active BP-lowering drug, as monotherapy or combination therapy, at any dose for secondary prevention in adults (≥18 years old) of both sexes with a diagnosis of ischemic stroke or TIA in which hemorrhage had been ruled out. We included all settings of care (e.g. acute or nursing homes, hospitals or

ambulatory, primary or secondary, inpatients or outpatients), and both acute or delayed treatments. RCTs comparing the effect of different doses of the same drug were excluded, except those that included another eligible comparator. We excluded also non-English-language study reports and RCTs designed to test a BP reduction strategy using several BP-lowering drugs of different classes rather than the efficacy of a specific BP-lowering drug.

Two authors independently selected the studies, extracted relevant information from the included studies (see the protocol registered in PROSPERO for details),[14] and assessed the study risk of bias. Any discrepancy was resolved by consensus and arbitration by the third author. We contacted study authors to retrieve outcome data not available in the full text.

Outcomes

Primary outcomes were all-cause mortality and the proportion of patients who developed a stroke following BP-lowering drug use, irrespective of its nature (ischemic or hemorrhagic) and severity. Secondary outcomes included: the proportion of patients who developed an ischemic stroke; an ischemic stroke or TIA irrespective of severity; a hemorrhagic stroke, defined as an acute extravasation of blood into and around the brain parenchyma (subdural hematoma and epidural hematoma were excluded); a cardiovascular event defined as any sudden death, fatal or non-fatal acute coronary syndrome, stroke, intracranial hemorrhage, or pulmonary embolism; a fatal cardiovascular event defined as any death due to any vascular cause, including unexplained sudden death; serious adverse events (SAEs) of hypotension, syncope, injurious falls, electrolyte abnormalities, bradycardia, or acute renal failure. We recorded the outcomes at the longest available follow-up for all analyses.

Study risk of bias, assessment and certainty of evidence

We evaluated the risk of bias for each included study using the criteria of The Cochrane Collaboration.[16] The following domains of bias were considered: selection (random sequence

generation, allocation concealment), performance (blinding of participants and personnel), detection (blinding of outcome assessment), attrition (incomplete outcome data), and selective outcome reporting. We explicitly judged the risk of bias in each criterion as 'low', 'high', or 'unclear'. We evaluated incomplete outcome data as having a low risk of bias when the numbers and reasons for dropouts were balanced (i.e. in the absence of a significant difference) between arms. Our assessment of methodological quality included published trial protocols when available. Finally, for each study, we explicitly judged also the overall risk of bias as follows: we considered allocation concealment, blinding of participants and personnel, blinding of outcome assessment and incomplete outcome data to classify each study as having low risk of bias when we judged all of the selected criteria as having low risk of bias; high risk of bias when we judged at least one criterion among those selected as having high risk of bias; and unclear risk of bias in the remaining cases. This appraisal was conducted by two reviewers independently, with conflicts resolved by the third reviewer. We examined the overall certainty of the evidence for primary and secondary outcomes using the GRADE framework methodology.[17] We used GRADEpro software for assessing the certainty of evidence.[18]

Statistical analysis

We estimated treatment effects from each study using the odds ratio (OR) with 95% confidence intervals (95% CIs). For our study, we had planned to perform a network meta-analysis.[14] However, due to the limited number of studies and scarce available data, the network meta-analysis was not feasible. For all outcomes with at least two studies, we performed standard pairwise meta-analyses with a random-effects model. We determined the presence of statistical heterogeneity by visual inspection of the forest plots and calculation of the I^2 statistic.[19] We performed subgroup analyses considering the following potential sources of heterogeneity (effect modifiers): inclusion limited to hypertensive patients (normotensive and hypertensive patients versus hypertensive patients only) or non-cardioembolic ischemic

strokes (all ischemic strokes versus non-cardioembolic ischemic strokes only), and time from the index ischemic event to randomization (acute patients treated within the first week versus stabilized patients treated after the first week). We performed sensitivity analyses for each primary and secondary outcome, including only trials that were classified as having a low risk of bias. All analyses were conducted with STATA version 16.0 (StataCorp, College Station, TX).

We presented the results from meta-analyses as summary OR and relative 95%CIs. We also reported absolute risk difference (ARD) estimates, calculated using as baseline the proportion of patients with an event in the control arm of the included studies, and applying the OR estimated in the meta-analysis to compute the absolute difference between the intervention and control arms. Relative (ORs) and absolute estimates (ARDs), and the certainty of the evidence were reported in a Summary of Findings Table.

RESULTS

From a total of 4,709 citations identified by the search, 62 articles were retrieved in full-text. Overall, 22 articles referring to 15 RCTs evaluated BP-lowering treatments for secondary prevention in patients with previous ischemic stroke or TIA and were included in our review (Fig. 1).

Seven RCTs included also hemorrhagic or undetermined strokes but did not report or provide separated outcomes for ischemic stokes only; consequently, they were excluded from the meta-analysis.[20-26] The characteristics of these seven studies are summarized in Supplementary Table I.

Finally, eight studies reported data suitable for our purpose and were included in the meta-analysis.[8,27-40] The characteristics of these eight studies are summarized in Table 1.

The eight RCTs included in the meta-analysis enrolled 33,774 patients with ischemic stroke or TIA, the mean follow-up was 25 months (range 3-48). Among the eight studies, two evaluated the use of BP-lowering drugs in acute stroke patients within 48 hours from stroke onset, with a follow-up between 3 to 6 months,[38-40] while the remaining six enrolled stabilized patients with a follow-up between 1 to 4 years. PATS,[8] PROGRESS[33,34] and SCAST[39] studies included also hemorrhagic and undetermined stroke cases, that were excluded from the meta-analysis. The studies were published between 1970 and 2015, males ranged between 57% and 72% (weighted mean 66%) and mean age from 60 to 71 years (weighted mean 65 years). Most studies included both hypertensive and normotensive patients and excluded patients with cardioembolic strokes (we included in this group also the PRoFESS study, reporting 1.8% cardioembolic strokes[35]). Different treatments were evaluated across studies included in the meta-analysis: three studies were on angiotensin II receptor blockers, one on angiotensin converting enzyme inhibitor with or without a diuretic, one on diuretic, one on beta-blocker, one on calcium channel blocker and one on a combination of 4 drugs.
Overall, only four trials were judged at low risk of bias (Fig. 2).

Not all RCTs contributed information to all outcomes. The study estimates and the pooled estimates of any BP-lowering treatment versus placebo/no treatment for each primary outcome are showed in Figure 3. The corresponding estimates for each secondary outcome are showed in Supplementary Figures I, II and III. Table 2 is the Summary of Findings Table and presents the relative and absolute estimates, and the certainty of evidence (GRADE assessment), for each primary and secondary outcomes.

Six RCTs, including 27,803 patients, evaluated all cause-mortality as outcome. Moderate-quality evidence due to study risk of bias indicated that mortality occurred similarly in patients taking any type of BP-lowering treatment compared with placebo, with an absolute

risk of 7.3% and 7.9% respectively (OR, 1.01 [95% CI, 0.92 to 1.10], I^2=0%; ARD, 0.1% [95% CI, -0.6 to 0.7%]).

Six RCTs, including 31,785 patients, evaluated all stroke as outcome. Moderate-quality evidence due to between-study heterogeneity indicated that a stroke (ischemic or hemorrhagic) occurred in 7.9% of patients taking any type of BP-lowering drug compared with 9.7% of patients taking placebo (OR, 0.79 [95% CI, 0.66 to 0.94], I^2=61%%; ARD, -1.9% [95% CI, -3.1 to -0.5%]).

Two RCT, including 5,507 patients, evaluated our secondary outcome ischemic stroke or TIA. High-quality evidence indicated that ischemic stroke or TIA occurred in 10.6% of patients on BP-lowering treatment compared with 13.2% of those on placebo (OR, 0.78 [95% CI, 0.66 to 0.91], I^2=0%; ARD, -2.6% [95% CI, -4.1 to -1.0%]).

The protective effect of BP-lowering treatment, although not statistically significant, can be also postulated for the following secondary efficacy outcomes: ischemic stroke, hemorrhagic stroke, cardiovascular event, and cardiovascular death.

Two RCTs, including 25,303 patients, evaluated the occurrence of serious adverse events. High-quality evidence indicated that these events occurred in 2.9% of patients taking any type of antihypertensive treatment compared with 2.3% of patients taking placebo (OR, 1.25 [95% CI, 1.07 to 1.46], I^2=0%; ARD, 0.6% [95% CI, 0.1 to 1.0%]).

Subgroup analysis including studies that compared angiotensin II receptor blockers with placebo did not show any significant effect of these drugs on our primary and secondary outcomes, except for increased occurrence of SAEs (data not published).

Results of the subgroup analyses in stabilized and non cardioembolic strokes were similar to those of the overall analysis, while the subgroup analyses in hypertensive patients as well as

the sensitivity analysis including only RCTs at low risk of bias were not statistically significant also for the “all stoke” primary outcome (Supplementary Table II).

DISCUSSION

In our systematic review, we found eight RCTs that enrolled ≈ 33,500 patients with ischemic stroke or TIA in developed countries, including Asia. Compared with other community-based studies on ischemic stroke,[41] here the mean age is slightly lower (65 years) and the male/female ratio a little bit higher (1.94) but, overall, the general characteristics of this population seem adequate for our purposes.

In this meta-analysis, which is the first that focused on patients qualifying with ischaemic stroke or TIA, the use of BP-lowering treatments was associated with a 1.9% risk reduction of stroke. Our results are in accordance with previous meta-analyses, based on RCTs that included patients with TIA or stroke, both ischemic and hemorrhagic,[7-11] and confirm the current guidelines and expert recommendations for the secondary prevention after ischemic stroke or TIA.[5,12,42,43] In particular, the absolute risk reduction is higher for new ischemic stroke or TIA (- 2.6%) rather than for new hemorrhagic stroke (-0.3%). However, BP-lowering agents seem to have less protective effective for recurrent ischemic stroke, as showed by the absolute risk reduction of -1%.

On the other hand, BP-lowering treatments increase the risk of SAEs by 0.6% and do not show any effect on the all-cause mortality risk. Mortality was not altered by BP-lowering treatments also in two other meta-analyses that considered this outcome in a similar combined sample size (respectively 15,527 and 35,110 patients).[7,11] However, if we consider cardiovascular deaths only, our results point to a possible protective effect of BP-lowering treatment, although not statistically significant (OR, 0.89 [95% CI, 0.77 to 1.01]), which is

indeed confirmed in two other larger meta-analysis that included also hemorrhagic strokes (risk ratio, 0.85 [95% CI, 0.75–0.96][10] and 0.85 [95% CI, 0.76–0.95][11]). These results suggest that BP-lowering treatments may reduce the risk of cardiovascular death also in patients with ischemic stroke or TIA but could slightly increase the risk of non-cardiovascular death.

These results were the first obtained in patients with ischemic cerebrovascular disease only, while previous meta-analysis, even in subgroup analysis, included also patients with hemorrhagic stroke in variable percentage (probably between 5% and 15% of the combined sample size).[7-11] Although ischemic and hemorrhagic strokes share some features qualitatively, especially when considering elevated BP as a risk factor, they differ quantitatively in several aspects. For example, while there is a lot of evidence supporting the use of BP-lowering treatments for secondary prevention in patients with TIA or stabilized ischemic stroke, there are still many concerns about the treatment of elevated BP in patients with acute ischemic stroke, due to impairment of cerebral autoregulation: while elevated BP is associated with an increased rate of hemorrhagic transformation, the ischemic tissue is also vulnerable to acute BP reduction, potentially leading to infarct growth.[44,45] On the contrary, in patients with acute intracerebral hemorrhage, the acute lowering of elevated systolic BP is recommended in most cases;[46] only recently, following the results of a single large RCT, some concerns were raised also for intensive BP lowering in patients with acute cerebral hemorrhage.[12] Furthermore, given the same BP-lowering agent and considering the risk reduction of major vascular events, patients with hemorrhagic stroke seem to have an increased benefit compared to patients with ischemic stroke.[34] Finally, the protective effect of intensive BP treatment on recurrent stroke seems higher in patients with previous hemorrhagic stroke rather than in those with ischemic stroke, although this difference is not statistically significant.[47]

Our meta-analysis has also some limitations, mainly due to the lack of data, and several questions remain unanswered. First, most of the RCTs included in this meta-analysis enrolled patients with stabilized, non cardioembolic ischemic stroke and our results cannot be broadened to acute patients and all ischemic strokes (irrespective of cardioembolic source). Second, two of the included RCTs (VENTURE and SCAST) have very short follow-up (3-6 months) and are probably more suitably designed to evaluate the effect of BP reduction on early vascular events. Third, our results support BP reduction irrespective of the initial BP level; unfortunately, we do not have data in normotensive patients only. Fourth, we decided to exclude RCTs designed to test a BP reduction strategy rather a specific antihypertensive drug; therefore, we do not have data neither on the degree of BP reduction nor on the target BP. Fifth, with this study, we aimed also at providing a ranking of the various drug classes via network meta-analysis but this was not feasible due to the limited number of studies and scarce available data. In our meta-analysis most of the evidence came from two RCTs (PATS and PROGRESS) that used a diuretic alone or in association with an angiotensin-converting-enzyme inhibitor, which are recommended also in the current guidelines.[5,12] Unfortunately, only one small RCT included in this meta-analysis tested a calcium channel blocker,[28] while there are evidences that these drugs are superior for the prevention of stroke.[48] Additional randomized controlled trials are need to answer these questions.

CONCLUSIONS

The results of our study support the use of BP-lowering treatments in secondary prevention after ischemic stroke or TIA, in particular when stabilized and without cardioembolic origin. BP-lowering treatments may reduce the risk of cardiovascular death but do not affect the all-cause mortality risk.

However, scanty data were available in order to provide robust results based on subgroup and sensitivity analyses, as by specific drug classes. Thus, additional RCTs are warranted.

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Disclosures

None.

Supplemental Materials

Online Figures I – III

Online Tables I – II

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Figure Legends

Figure 1. Study selection.

Figure 2. Risk of bias of the included studies

Figure 3. Forest plots of meta-analysis estimates of any BP-lowering drug against placebo/no treatment for primary outcomes

Legend: CI, confidence interval; θ, treatment effect

Table 1. Characteristics of the studies included in the meta-analysis

Legend: TIA, transient ischemic attack; TR, to randomization; CE, cardio-embolic; HP, hypertensive patients; NA, not available

Study (year)	Index event (patients, n)	Intervention and control	Country	Time TR	Follow-up, mean	Non-CE only	HP only	Age, mean	Males, %
Carter (1970)[27]	Ischemic stroke (99)	Methyldopa or bethanidine or debrisoquine, with or without thiazide diuretics vs. No treatment	United Kingdom	> 14 days	4 years	Yes	Yes	NA (range 40 to 79)	57
Martí Massó (1990)[28]	Ischemic stroke or TIA (264)	Nicardipine 60 mg/day vs. No treatment	Spain	< 1 year	1 year	Yes	No	62	71
Dutch TIA (1993)[29,30]	Ischemic stroke or TIA (1,473)	Atenolol 50 mg/day vs. Placebo	Holland	< 3 months	32 months	Yes	No	NA (52% > 65 years)	64
PATS (1995)[8,31]	Ischemic stroke or TIA (4,245)	Indapamide 2,5 mg/day vs. Placebo	China	> 4 weeks	2 years	Yes	No	60	72
PROGRESS (2001)[32-34]	Ischemic stroke or TIA (5,243)	Perindopril 4 mg/day with or without indapamide 2.5 mg/day vs. Placebo	World	< 5 years	4 years	No	No	64	70
PRoFESS (2008)[35-37]	Ischemic stroke (20,332)	Telmisartan 80 mg/day vs. Placebo	World	< 120 days	30 months	Yes	No	66	64
SCAST (2011)[38,39]	Ischemic stroke (1,725)	Candesartan at fixed-dose escalation scheme (4 mg on day 1, 8 mg on day 2, and 16 mg on days 3–7) vs. Placebo	North Europe	< 30 hours	6 months	NA	Yes	71	58
VENTURE (2015)[40]	Ischemic stroke (393)	Valsartan 80 mg/day for the first 2 days, then increased if required vs. No treatment	South Korea	24-48 hours	90 days	No	Yes	65	59

Table 2. Summary of findings for primary and secondary outcomes

Any BP-lowering drug compared to placebo/no treatment in patients with ischemic stroke or transient ischemic attack

Outcome № of participants (n° of studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		Without BP-lowering drug	With BP-lowering drug*	Difference	
All-cause mortality № of participants: 27,803 (6 RCTs)	**OR 1.01** (0.92 to 1.10)	7.9%	**7.3%** (7.3 to 8.6)	**0.1% more** (0.6 fewer to 0.7 more)	⨁⨁⨁◯ MODERATE [a]
All strokes № of participants: 31,785 (6 RCTs)	**OR 0.79** (0.66 to 0.94)	9.7%	**7.9%** (6.2 to 9.2)	**1.9% fewer** (3.1 fewer to 0.5 fewer)	⨁⨁⨁◯ MODERATE [b]
Ischemic stroke № of participants: 26,232 (4 RCTs)	**OR 0.87** (0.70 to 1.08)	8.4%	**7.4%** (6.1 to 9.1)	**1.0% fewer** (2.4 fewer to 0.6 more)	⨁⨁◯◯ LOW [b,c]
Ischemic stroke or TIA № of participants: 5,507 (2 RCTs)	**OR 0.78** (0.66 to 0.91)	13.2%	**10.6%** (9.2 to 12.2)	**2.6% fewer** (4.1 fewer to 1 fewer)	⨁⨁⨁⨁ HIGH
Hemorrhagic stroke № of participants: 25,968 (3 RCTs)	**OR 0.70** (0.46 to 1.08)	0.8%	**0.6%** (0.4 to 0.9)	**0.3% fewer** (0.5 fewer to 0.1 more)	⨁⨁⨁◯ MODERATE [c]
Cardiovascular events № of participants: 27,450 (5 RCTs)	**OR 0.92** (0.77 to 1.09)	14.8%	**13.8%** (11.8 to 15.9)	**1.0% fewer** (3 fewer to 1.1 more)	⨁⨁◯◯ LOW [b,c]
Fatal cardiovascular event № of participants: 26,643 (5 RCTs)	**OR 0.89** (0.77 to 1.01)	3.6%	**3.2%** (2.8 to 3.6)	**0.4% fewer** (0.8 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE [c]
Serious adverse events № of participants: 25,303 (2 RCTs)	**OR 1.25** (1.07 to 1.46)	2.3%	**2.9%** (2.5 to 3.3)	**0.6% more** (0.1 more to 1 more)	⨁⨁⨁⨁ HIGH

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio; **TIA**: transient ischemic attack

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. study with high risk of bias
b. presence of heterogeneity
c. imprecision in the estimate