South African National Essential Medicine List
Primary Healthcare Medication Review Process
Component: Central nervous system conditions

MEDICINE REVIEW SUMMARY

Executive Summary

Date: March 2018
Medicine (INN): Aspirin (Acetylsalycylic acid)
Medicine (ATC): B01AC06
Indication (ICD10 code): G45.0-4/G45.8-9/I63.0-6/I63.8-9/I64
Patient population: Adult patients with acute onset of stroke of unknown aetiology
Prevalence of condition: Stroke is the third most common cause of death (6.5% of all deaths) after HIV/AIDS and ischaemic heart disease in South Africa (age-standardised mortality of stroke for both males and females in 2000 was 125 per 100 000). Specifically, the age-standardised prevalence of stroke is 290 per 100 000, and the crude prevalence is 300 per 100 000 (95% confidence interval (CI) 250 - 357 per 100 000)[i]
Level of Care: Primary level of care
Prescriber Level: Nurses
Current standard of Care: Nil
Efficacy estimates: (preferably NNT) NNT=79; NNTH=574[ix]
Motivator/reviewer name(s): Dr T Gengiah; Ms TD Leong
PTC affiliation: None

Name of author(s)/motivator(s): Dr T Gengiah; Ms TD Leong

Author affiliation and conflict of interest details:
Dr T Gengiah: CAPRISA – AIDS research organization; Primary Health Care Committee member; No conflicts of interest
Ms TD Leong: National Department of Health, Essential Drugs Programme; Secretariat to the Primary Health Care Committee and National Essential Medicines List Committee; No conflicts of interest

Question:
What is the safety and efficacy of a pre-referral dose of aspirin in acute stroke of unknown aetiology at primary level of care in the South African setting?

Summary of findings:
Stroke epidemiology in SSA

Cerebrovascular diseases including stroke is among the top 4 causes of death in South Africa (Stats SA, 2017). Black women have the highest mortality rate due to stroke (160 per 100 000), while mortality was lowest in white men (72 per 100 000). Ischaemic stroke (IS) (85%) caused by an embolus or thrombosis, is more common than intracerebral haemorrhage (ICH) (15%), caused by the rupture of a cerebral vessel with bleeding into the brain[ii]. In a hospital-based stroke series, cerebral haemorrhage (mainly the result of hypertension) was found twice as often in black (28%) as in white (15%) stroke

patients[iii], which is typical of the findings from other South African[iv] and African[v] hospital-based stroke studies that have found ICH in around a third of black stroke patients. Although the incidence of stroke increases with increasing age in the black South African population as in other population groups, some studies have found that the incidence of stroke in younger age groups (35 - 54 years) is higher than that found in other populations[vi]. Furthermore, stroke management –particularly in young South Africans – is complicated by the high prevalence of human immunodeficiency virus (HIV) which appears to increase risk for IS[vii viii].

Evidence summary

ARTICLES	STUDY DESCRIPTION	EFFECT SIZE	CONCLUSION
i) Meta-analysis			
Sandercock, et al[ix] CAST, 1997[x] IST, 1997[xi]	Meta-analysis: 8 trials, aspirin (4 studies), aspirin +dipyridamole (1 study), ticlopidine (3 studies) N=41, 483 participants Treatment duration: 5 days – 3 months 98% of data came from the CAST, 1997 (9) and IST, 1997 (10) trials where several patients only had a CT scan post randomization and received aspirin before CT was confirmed (n=205/20427 in aspirin arm vs 168/20423 control arm).	Meta-analysis: Aspirin 160 - 300 mg started within 48 hours of onset provided a significant decrease in death OR: 0.95 (95%CI: 0.91-0.99). NNT=79 Overall odds of ICH was 1.22 (95%CI: 1-1.5), NNTH=574 IST: Aspirin produces 2 (SD 1) transfused or fatal extracranial bleeds per 1000.	In presumed IS, aspirin saved lives and reduced the risk of further strokes in the first two weeks. The risk vs benefit shows that aspirin treatment in acute stroke is warranted
Rothwell et al [xii]	Pooled analysis of individual level patient data from all RCTs of aspirin vs control, post TIA or IS (n=15 778, n=12 trials) and pooled data from trials where randomization occurs <48hrs after major acute stroke (n=40 531, 3 trials)	Aspirin ↓6 week risk of recurrent stroke by 60% [HR] 0.42, 95% CI 0.32–0.55, p<0·0001) and disabling or fatal IS by about 70% [HR] 0.29, 0.20–0.42, p<0.0001. Aspirin↓ recurrent IS at 14 days in patients with less severe baseline deficits, substantial by the second day after starting treatment (2–3 day HR 0.37, 95% CI 0.25–0.57, p<0.0001).	Aspirin ↓ severity of all stroke types and in MI. After TIA and minor stroke – aspirin provides considerable benefit – even advocate self-administration as early phase of secondary prevention.
ii) Decision analysis model			
Berkowitz et al [xiii]	Decision -analysis Data from CAST and IST. Across both trials, 773 patients whose stroke was due to ICH were inadvertently randomized to aspirin (398) or placebo (375), were included in the model	The model estimates with ICH as the base case scenario, aspirin is predicted to: ↓ in-hospital mortality by 4 per 1000, NNT=250, ↓ second in-hospital stroke by 8 per 1000, NNT=125 ↓ combined risk of in-hospital mortality or second stroke by 13 per 1000, NNT=77	Aspirin administration is favored even when acute stroke is of unknown aetiology. See also cohort study of 148 patients in the Gambia – estimate 46% had hemorrhagic stroke and benefitted from aspirin therapy

Currently, the REstart trial is underway that will be concluded in 2019[xiv]. This RCT will provide further information on the risks of antiplatelet or anticoagulant therapy post stroke due to intracerebral haemorrhage.

Evidence quality

Sandercock et al: Cochrane review showed a significant, but modest benefit of antiplatelet therapy vs control in acute presumed ischaemic stroke in reducing death or dependence at end of follow up.

The study question was clear and search strategy was comprehensive with no language restrictions. The review process conducted by two reviewers to reduce errors and bias. Funnel plot assessments did not suggest substantial publication bias in respect of the primary outcomes.

The review included RCTs that investigated various antiplatelet agents, but two RCTs testing aspirin 160 mg to 300 mg daily, started within 48 hours of the onset of stroke symptoms, contributed 9% of the data. Attrition bias, however, was associated with both the CAST and IST RCTs. This bias and the open design of the IST trial may have underestimated or overestimated results of this review.

Potential conflict of interest of authors noted, but declared.

Rothwell et al: Meta-analysis of pooled data from 3 RCTs by Rothwell et al (2016)[xii] showed a modest overall effect of aspirin vs control in reducing the 14 day risk of recurrent ischaemic stroke. However, there was significant heterogeneity according to baseline stroke severity (p_{het}=0.014) See Figure 1, below[xv]. (Pooled estimates were either obtained by fixed-effects meta-analysis (Mantel-Haenszel-Peto method), with no significant heterogeneity determined between trials if $p_{het} > 0.05$ on the χ^2 test; or by random effects meta-analysis).

Aspirin was shown to reduce the 14 day risk of recurrent ischaemic stroke in patients with mild or moderate neurological deficits at baseline (OR 0.51, 95% CI 0.34 to 0.75; p=0.0007; p_{het}=0.85 and OR 0.65, 95% CI 0.44 to 0.98; p=0.040; p_{het}=0.039, respectively). However, there was no effect for those with severe neurological damage (OR 1.10, 95% CI 0.77 to 1.58; p= 0.60; p=0.50)
Amongst patients with mild and moderate stroke, the early administration of aspirin within the first 2 to 6 days showed a greater benefit in reducing recurrent ischaemic stroke (See Figure 2, below [xii]).

The review addressed clear questions. However, details of the literature search were not provided and it is uncertain how many of the authors were actively involved in the study selection, quality assessment and data extraction processes. Trials were heterogeneous regarding baseline stroke severity, as described above and also differed in duration of randomised treatment allocation. Study was funded by the Wellcome Trust and the National Institute of Health Research (NIHR) Biomedical Research Centre, Oxford.

Meta-analysis of the effect of aspirin vs control on the 14-day risk of recurrent ischaemic stroke in trials of aspirin in treatment of acute stroke stratified by the extent of the initial neurological (mild, moderate or severe).
Heterogeneity between 3 severity groups: p=0.014

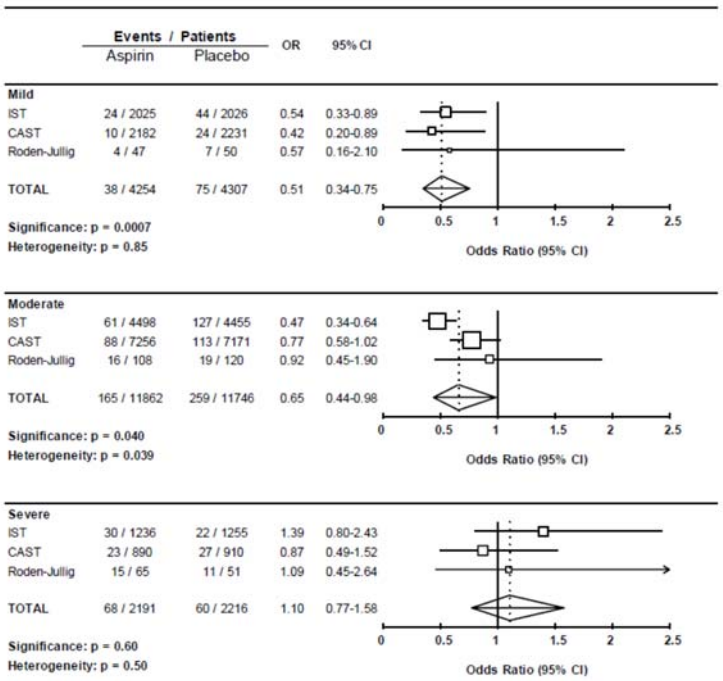

Figure 1: Supplementary appendix 9 of Meta-analysis by Rothwell et al, 2016

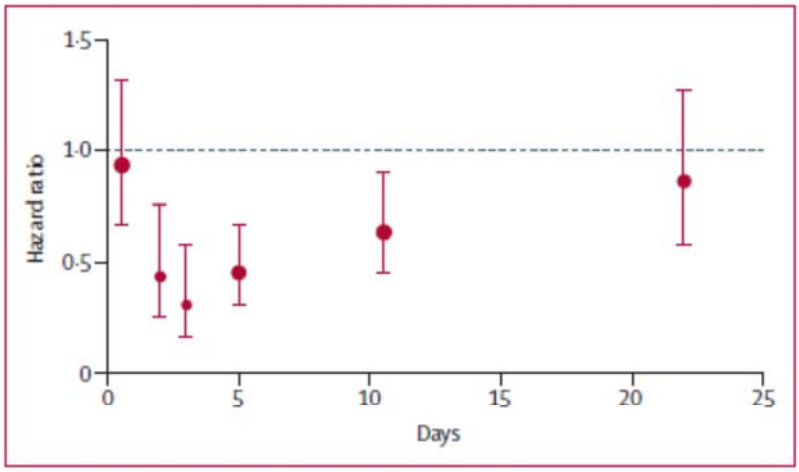

***Figure 4*: Pooled hazard ratios for the effect of aspirin versus control on risk of recurrent ischaemic stroke in patients with mild and moderately severe initial neurological deficits during early follow-up in Chinese Acute Stroke Trial and International Stroke Trial**[20,21]

Data plotted at median timepoint for the following follow-up periods from randomisation: days 0–1, days 2–3, days 4–6, days 7–14, after 15 days. Error bars show 95% CIs. This analysis excludes 3292 (21%) patients with mild or moderately severe stroke in the International Stroke Trial who had received aspirin during the days before randomisation. The equivalent analysis with these patients included is in appendix p 6.

Figure 2: Pooled hazard ratios for the effect of aspirin vs control on risk of recurrent ischaemic stroke in patients with mild and moderately severe initial neurological deficits during early follow-up (days 0-1; 2-3,4-6; 7-14; >15) in two large trials of aspirin in treatment of acute stroke.

Conclusion

The evidence for the benefit of aspirin within 48 hours of stroke is modest but significant. In the event of the delays in accessing CT scans, which is common in SA, it is reasonable to suggest that in the absence of imaging and confirmation of diagnosis of stroke type, a pre-referral dose of aspirin in presumptive ischaemic stroke (where patient not currently on antiplatelet/antithrombotic therapy) be administered at the PHC clinic. Aspirin may be continued or discontinued in hospital depending on radiological findings.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	**SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS**
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [x] Not confident [ ] Uncertain [ ]	Sandercock et al (2014) [ix] Rothwell et al (2016) [xii]
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [x] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	Sandercock et al (2014) [ix] Rothwell et al (2016) [xii]
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X] List the members of the group. List specific exclusion from the group:	Rationale for therapeutic alternatives included: References: Rationale for exclusion from the group: References:
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	

RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [X] Uncertain [ ]	Cost of medicines/ month: **Medicine** | **Cost (ZAR)** Aspirin 300mg tablet, single dose | 0.39* * Contract circular HP09-2016SD **Additional resources:** n/a
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [x] Uncertain [ ]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[ ]	[ ]	[ ]	[ ]	[X]

Recommendation

Based on this evidence review, the Primary Health Care Committee recommends a pre-referral dose of aspirin 300 mg for acute presumptive ischaemic stroke, presenting at primary level of care.

Rationale: Evidence of a moderate benefit of aspirin outweighing harms of aspirin as a pre-referral dose in reducing recurrent ischaemic stroke of unknown aetiology.

Level of Evidence: I Meta-analyses [ix xii]

Review indicator:

Evidence of efficacy [ ] Evidence of harm [X] Price reduction [ ]

VEN status:

Vital [X] Essential [ ] Necessary [ ]

Monitoring and evaluation considerations

Safety monitoring

Research priorities

Safety of antiplatelet therapy at the time of intracerebral haemorrhage

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