South Africa National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Nephrology

MEDICINE REVIEW:

1. **Executive Summary**

Date: March 2018
Medicine (INN): Angiotensin receptor antagonists
Medicine (ATC): C09CA07 (1)
Indication (ICD10 code): I10-I15 Hypertensive diseases (2)
Patient population: Patients with a history of angiotensin-converting enzyme (ACE) inhibitor associated angioedema
Prevalence of condition: Angioedema occurs in approximately 0.1% to 0.5% of patients taking ACE-inhibitors (2). In a study looking at US veterans, 0.2% of patients developed ACE-inhibitor associated angioedema; the incidence rate was 1.97 (1.77 to 2.18) cases per 1000 person years (3)
Level of Care: Secondary level
Prescriber Level: Doctor
Current standard of Care: Cautionary provided not to use ARBs in patients with a history of ACE-inhibitor induced angioedema.
Efficacy estimates: (preferably NNT) n/a
Motivator/reviewer name(s): Dr V Mpongoshe, Ms TD Leong, Prof AG Parrish, Mr A Gray
PTC affiliation: N/A

2. **Name of author(s)/motivator(s) :**

Primary reviewers: Dr V Mpongoshe, Ms TD Leong
Secondary reviewers: Prof AG Parrish, Mr A Gray

3. **Author affiliation and conflict of interest details**

Primary reviewers:
Dr V Mpongoshe: Government Employees Medical Scheme, Adult Hospital Level Committee (2017-2019); no conflicts of interest.
Ms TD Leong: National Department of Health, Essential Drugs Programme; Secreteriat to the Adult Hospital Level Committee (2017-2020); no conflicts of interest.

Secondary reviewers:
Prof AG Parrish: National Essential Medicines List Committee (2016-2020); no conflicts of interest.
Mr A Gray: National Essential Medicines List Committee (2016-2020); insignificant conflict of interest.

4. **Introduction/ Background**

Initially when the nephrology chapter was under review, an external reviewer motivated for the use of telmisartan in patients that experienced angioedema on an ACE-inhibitor (ACE-I), submitting the TRANSCEND randomised controlled trial (RCT) as supporting evidence. The RCT showed no significant difference in

incidence of angioedema between the study arms (telmisartan 2 (0.07%) vs placebo 3 (0.1%); p=0.660) – see table below (1).

	Telmisartan (n=2954)	Placebo (n=2972)	Relative risk	p value
Total number of discontinuations (temporary or permanent)	1090 (36·9%)	1143 (38·5%)	0·96	0·215
Number of patients with permanent discontinuations	639 (21·6%)	705 (23·7%)	0·91	0·055
Hypotensive symptoms	29 (0·98%)	16 (0·54%)	1·82	0·049
Syncope	1	0		
Cough	35 (0·51%)	18 (0·61%)	0·84	0·613
Diarrhoea	7 (0·24%)	2 (0·07%)	3·52	0·094
Angio-oedema	2 (0·07%)	3 (0·10%)	0·67	0·660
Renal abnormalities	24 (0·81%)	13 (0·44%)	1·86	0·067

*Most discontinuations were for non-specific reasons, with little difference between the two groups for any specific category.

Table 2: Discontinuation of study medications and selected reasons for permanent discontinuations*

The TRANSCEND RCT was then reviewed:

Author, date	***Type of study***	**n**	**Population**	**Comparators**	**Primary outcome**	**Effect sizes**	**Comments**
(1) TRANSCEND Investigators, 2008	Randomised, placebo controlled, phase 3 study	5926	Patients intolerant to ACE-I, with established CV (coronary artery, peripheral vascular or cerebrovascular disease) or diabetes with end organ disease	Placebo	Composite of CV death, MI, stroke or hospitalization for heart failure	465 (15.7%) vs 504 (17.0%) HR for primary endpoint 0.92, 95% CI 0.81-1.05, p=0.216	There was no statistically significant improvement in primary outcome between telmisartan and placebo. There was no statistically significant difference in key secondary outcome when adjusted for multiplicity. Total mortality was similar (12.3% vs 11.7%; p=0.491) Most common reason for intolerance to ACE-I was cough (5225 participants, 88.2%), followed by symptomatic hypotension (244, 4.1%), angio-oedema or anaphylaxis (75, 1.3%), renal dysfunction (58, 1.0%) and other reasons 492, 8.3%). Very few patients included had a history of angioedema. There was no significant difference in incidence of angioedema necessitating discontinuation of medication between the study arms (telmisartan 2 (0.07%) vs placebo 3 (0.1%); p=0.660) – see table above.

The purpose of this technical medicine review is to assess available safety evidence of ARBs in patients who have a history of ACE-I associated angioedema.

5. Purpose/Objective i.e. PICO question

-P *(patient/population):* Adult patients intolerant to angiotensin-converting enzyme inhibitor (ACE-I) therapy, due to previous ACE-I associated angioedema
-I *(intervention):* ARBs
-C *(comparator):* N/A
-O *(outcome):* Angioedema

Question:

6. Methods:

a. Data sources: i) Pubmed
ii) Tripsdatabase

i) Pubmed

Search strategy: ((((angiotensin converting enzyme inhibitors) OR ACE Inhibitors) AND Angiotensin receptor blockers) OR ARB) AND Angioedema Filters: Clinical Trial; published in the last 10 years; Humans

11 items were retrieved, but none were relevant.

ii) Tripdatabase

Search strategy: "angioedema" and "angiotensin receptor blockers", restricted to systematic reviews.

9 systematic reviews were retrieved, of which 4 were relevant.

c. **Excluded studies:**

Author, date	*Type of study*	*Reason for exclusion*
B T Straka et al, 2017	Double-blind, placebo-controlled study	Not applicable to the research question (Combination ACE-I and ARBs) instead looked at Bradykin receptor blockers in pts with ACE-I induced angioedema
R Sinertet al, 2017	Phase 3, 2-armed , randomized double-blind clinical trial	Not applicable to the research question (Combination ACE-I and ARBs) instead looked at Bradykin receptor blockers in pts with ACE-I induced angioedema
M Senniet al, 2016	ulticentre, randomized, double-blind study	Not applicable to the research question (Combination ACE-I and ARBs) instead looked at tolerability of Sacubitril/valsartan in HF pts, ACE-I induced angioedema was an exclusion
M Bas et al, 2015	Phase 2, randomized double-blind clinical trial	Not applicable to the research question (Combination ACE-I and ARBs) instead looked at Bradykin receptor blockers in pts with ACE-I induced angioedema
M A Sabe et al, 2015	Doble-blind, randomized controlled trial	Not applicable to the research question (Combination ACE-I and ARBs) instead looked at comparing Sacubitril/valsartan and Enalapril HF pts
J J McMurray et al, 2014	Doble-blind, randomized controlled trial	Not applicable to the research question (Combination ACE-I and ARBs),excluded pts with history of ACE-I angioedema
Lakhdar et al, 2008	Systematic review and meta-analysis	Not applicable to the research question (Combination ACE-I and ARBs)
Costa-Scharplatzet al, 2007	Economic Evaluation	Not applicable to the research question
Musini et al, 2017	Systematic review and meta-analysis	Only alkiserin (vs placebo) was reviewed
Bolignano et al, 2015	Systematic review and meta-analysis	Not applicable to the research question
Musini et al, 2017	Systematic review and meta-analysis	Updated version available
Kuenzli et al, 2010	Systematic review and meta-analysis	Not applicable to the research question (Combination ACE-I and ARBs)
Boulware et al, 2001	Economic evaluation	Not applicable to the research question

d. Evidence synthesis

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
(7) Zou et al, 2009	Systematic review and meta-analysis	28 studies; n=5157	Patients with hypertension, with or without other diseases such as metabolic syndrome and chronic kidney diseases;	Telmisartan versus ACE-Is, used as monotherapy	Outcome variables: at least one of BP, therapeutic BP response rates, mortality, cerebrocardiovascular event rates, adverse events, withdrawal and cough was reported.	2 ADRs of angioedema in enalparil and 2 in Lisinopril; none in telmisartan group	Unsure whether search was restricted to published articles; but appropriate steps taken to minimize bias and duplication. Quality assessed using Jadad scoring system. Only four reports of angioedema reported with enalapril and lisinopril and none with telmisartan; larger studies and research of other ARBs' association with angioedema are required.
(2) Makani et al, 2012	Systematic review and meta-analysis. Mean trial follow-up: 123 weeks	40 RCTs; n=206,596; of ≥ particpants ; ≥8 weeks duration	Patients on ACE-I, ARBs or direct renin-inhibitors.	ACE-I, ARBs or direct renin-inhibitors vs other antihypertensives or placebo or each other.	Angioedema	Angioedema: - ACE-Is vs ARBs - OR 2.24, 95% CI 1.50 to 3.34; 7 RCTs -ACE-Is vs placebo - OR 2.79, 95% CI 1.63 to 4.79; 10 RCTs - ARBs vs placebo - OR 1.18, 95% CI 0.39 to 3.61; seven RCTs. Subgroup analyses: Incidence of angioedema: - ACE inhibitors: significantly highera mongst African Americans, heart failure, RCTs with high risk of bias, RCTs of < 1 year. - ARBs: significantly higher in heart failure, RCTs with high risk of bias, RCTs < 1 year duration; **but not amongst those with ACE-I intolerance.**	Review was restricted to published RCTs; possible risk of publication bias; but RCTs in multiple languages were searched in multiple databases. Bias minimized with regards to data extraction; but unsure of steps taken regarding data selection and assessment. Risk of bias in individual RCTs not reported. Quality of RCTs assessed using Cochrane Collaboration tools. Pooled RCTs were heterogenous - populations with different underlying risks, and not from direct comparisons; and risk may have been underestimated as some RCTs only reported common ADRs (>1%); some had a run-in phase prior to randomization (where angioedema may have occurred); some RCTs excluded ACE-I induced angioedema. **Authors mention that larger RCTs required to evaluate risk of ARB-associated angioedema amongst those with history of ACE-I-associated angioedema.**

(8) Caldeira et al, 2012	Systematic review and meta-analysis.	11 RCTs; n=12.632	Patients with intolerance to ACE-Is.	ARBs vs ACE-Is, diuretics, placebo; I RCT comparing low dose vs high dose ARB.	Discontinuation due to adverse events (cough, angioedema/anaphylaxis, Hypotension, renal dysfunction and hyperkalaemia).	<u>Angiodema:</u> No significant difference between ARBs and placebo. RR 1.62, 95% CI 0.17 to 15.79; I2=46% **Previous angioedema:** **- ARBs vs placebo: RR 3.01 (95% CI 0.41 to 22.39); event rate 4.1 vs 0.8**	Various relevant databses searched. No language bias, but possible publication bias (as only published RCTs reviewed). Steps taken to minimize risk of bias for study selection, data extraction; but unsure if more than one reveiwer assesed quality of RCTs. Appropiate assessment of quality of RCTs (Jadad tool used). Heterogeneity across RCTs regarding methodology and definitions of adverse events. Review shows a trend towards no association of angioedema with ARBs; however, although TRANSCEND RCT (n=2954) had 2ADRS reports of angioedema with telmisartan; CHARM-alternative RCT(n=1013) had 3 ADRS of angioedema reported with candesartan. Authors also mentioned the HEALL trial with 6 events of angioedema associated with higher dose losartan, but none for low dose losartan (50 mg). As angioedema is a serious life-threatening ADR, caution of the risk of angioedema with ARBs should be considered, though reported to be lower than that of ACE-Is.
(9) Haymore, 2008	Systematic review and meta-analysis.	1 RCT and 2 observational studies; n=71 The median follow-up times:11 to 33.7 months.	Previous history of ACE-I induced angioedema and on subsequent ARB. Mean age: 63 years. Men: 40 to 68.2%. Caucasian: 23 to 88.4%.	No comparators.	Possible and confirmed angioedema.	**Possible angioedema cases:** **- Risk 9.4% (95% CI 1.6 to 17).** **Confirmed angioedema cases:** **- Risk 3.5% (95% CI 0.0 to 9.2).** **No fatal events due to angioedema with ARBs.** **Statistically significant heterogeneity between the studies.**	Research question was clear; search was comprehensive; but no control group comparator in selected studies. Risk of bias cannot be ruled out as only 1 study was a RCT, the other 2 were observational studies. Methods for minimizing risk and error and quality assessment not reported. Studies heterogenous, and differences in interventions and regimens not reported. Studies underpowered and reported angioedema events were small and may result in error. Limited evidence suggesting a low risk of angioedema associated with ARBS in patients with a history ACE-I induced angioedema should be interpreted with caution, as overestimation of results possible due to low methodological quality of this review.

e. Evidence quality:

There is limited evidence demonstrating absolute safety use of ARB in patients with ACE-inhibitor associated angioedema. There appears to be less incidence of cross-reactivity of angioedema of patients who received ARB after experiencing ACE-I induced angioedema, but the evidence is of poor methodological quality (9).

f. Pharmacovigilance data

Vigibase™ database was accessed on 13 September 2018 and it was noted that Uppsala Monitoring Centre had received 10057 ADR reports for telmisartan (40% from the Americas with a distribution of 53% amongst females and 43% amongst males). Of these 184 were for angioedema. Despite the concerns about the quality of the Vigibase™ data, the caution of angioedema with ARBs in patients with a history of ACE-inhibitor associated angioedema seems warranted (12).

7. Alternative agents: N/A

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: [ ] Not confident: [X] Uncertain: [ ]	Limited data – despite the systemic review by Caldeira et al, 2012, assessing 12 RCTs, only 3 RCTs looked at angioedema as a reason for intolerance .
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: [x] Harms outweigh benefits: [ ] Benefits = harms or Uncertain: [ ]	Caution against ARBs in patients with a history of ACE-inhibitor induced angioedema is preferable.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes: [ ] No: [X]	
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: [ ] No: [ ] Uncertain: [X]	
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [ ] Uncertain: [X]	
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 Adult Hospital Level Committee does not recommend the removal of the caution of angioedema associated with ARBs in patients with a history of ACE-inhibitor induced angioedema.

Rationale: Limited evidence appears to suggest that cross reactivity with an ARB after ACE-I associated angioedema appears to be low. However, low methodoloogical quality of this evidence precludes the Committee from confidently recommending ARBs in patients with a history of ACE-induced asosociated angioedema.

Level of Evidence: II Systematic reviews and meta-analyses

Review indicator:

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

VEN status:

Vital	Essential	Necessary
[ ]	[X]	[ ]

Monitoring and evaluation considerations

Research priorities

References:

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