7. SUMMARY AND CONCLUSION

7.1. Summary of the study

➢ The present study provides mechanistic evidence of the neuroprotective effects of ACEIs and ARBs against cognitive decline thus supporting the ‘Angiotensin II’ hypothesis of cognitive impairment.

➢ RAS has ample documentation as a key player in mediating the complex of integrated neurological and behavioural activities seen in AD, and angiotensin-II activity is believed to be inversely associated with learning and memory. The putative mechanisms include disruption of cholinergic function, induction of inflammation and ROS generation in the brain, and reduction in CBF, which in turn leads to cerebrovascular dysfunction associated with neuronal loss in the hippocampus.

➢ Pharmacological modulation of RAS has previously been shown to be valuable in reducing the memory deficits in animal models of AD and also in observational studies and clinical trials. In particular, ARBs and ACEIs which are active in brain RAS can abolish the unfavourable effects of Ang-II and lead to restoration of cholinergic function and recovery of cerebrovascular function associated with a significant reduction in oxidative stress.

➢ In the present study, the use of ACEIs and ARBs have shown preliminary experimental promise in reversal of scopolamine-induced amnesia which is one of the well-established and most widely used models to study the behavioural and cognitive deficits seen in AD.

➢ In-depth analysis of literature fails to investigate the differential role of structurally heterogeneous ACEIs and ARBs on cognitive function. In the current study, we made an attempt to address the effects of structurally different ACEIs and ARBs on cognitive function with emphasis on learning and memory, cholinergic activity, antioxidant
activity, alteration in hippocampal morphology and degree of neuronal survival following induction of amnesia with the muscarinic antagonist, scopolamine.

➢ The study has also thrown light on the differential effects observed between members of the drug class, indicating that although ACEIs and ARBs as a class share the same mechanism of action, they are not identical and exhibit molecule-specific effects that may be mediated by mechanisms which are not solely dependent on their interaction with ACE or AT1 receptors. These effects can be attributed to distinct differences in chemical structures and pharmacokinetic features, which helps underscore why these agents should not be assumed to have similar effects on all biological pathways beyond the RAS.

➢ From the present findings, it can be suggested that the chemical classification of ACEIs and ARBs based on structure, to a certain extent, may help in identifying other drug-specific mechanisms that may prove important for different clinical conditions. Further, the effective dose of an ACEI or ARB for different indications may also vary. While a compound’s ability to cross the blood brain depends on its size, charge and lipophilicity, the integrity of BBB and the dose of the medication could also influence its central activity.

➢ Cognitive impairment is the most common manifestation in AD. Considering the prevalence rates of AD and the fact that its nature presents with a severe burden on the life of patients and caretakers, development of drugs that can minimize the cognitive deficits in AD is imperative.

➢ The majority of therapeutic approaches such as AChEIs offer replacement therapy to augment the functioning of defective neurotransmitter systems in AD. However considering the multifactorial pathology of AD, development of strategies or identification of biological targets that alter its underlying pathology and progression could be the next best approach. In this regard, therapeutic use of agents to modulate
Ang-II and AT<sub>1</sub> receptor activity in cardiovascular medicine has provided insight into potential, alternative uses for these agents, including dementia.

- Studies over the past two decades have revealed significant contributory functions of RAS in the pathogenesis of AD, including alterations to ACE and other angiotensin related components of the RAS, and treatment with RAS inhibitors is expected to confer therapeutic benefits in AD. Our study adds important evidence to the beneficial effects of pharmacological modulation of RAS pathway on learning and memory and especially the underlying mechanisms that mediate these effects. It also throws some light in elucidating the differential effects of different agents within the same class. However, further studies are warranted to offer more meaningful comparisons between ACEIs and ARBs in terms of cognitive enhancement.

- Since RAS inhibitors are one of the commonly used drugs for hypertension, they may play an important role in preventing the memory deficits in elderly patients with both hypertension and dementia, which needs to be well investigated in the clinical settings.

### 7.2. Limitations of the Study

The present study indicates the positive correlation between RAS inhibitors and memory enhancement. This has been demonstrated by studying the behavioral, biochemical and neuropathological changes mediated by ACEIs and ARBs in a model of memory impairment induced by injection of scopolamine in rats. Scopolamine-induced amnesia is considered as one of the most extensively used experimental animal models in research to screen for drugs with potential therapeutic value in dementia. However, extrapolation of these results directly to humans may be difficult as this is an animal experimentation, and therefore there is a need for further validation of these current findings in clinical settings.
7.3. Scope for future work

Future works may be undertaken in the following direction:

- Estimation of ACE activity in the brain following induction of amnesia, and analysing the expression of brain angiotensin receptor and ACE mRNA expression may prove useful to assess the extent of penetration of ACEIs/ARBs into the brain.

- Since Ang-IV is believed to be partly involved in mediating the beneficial effects of RAS inhibitors, measuring the level of Ang-IV in the brain may add further significance to the above findings.

- The role of these centrally acting ACEIs and ARBs in scopolamine induced memory impairment and its correlation with brain energy metabolism and cerebral blood flow can be studied.

- Evaluating the neurotransmitters and neurotrophin levels during treatment with ACEIs and ARBs would give much clearer understanding of the effect of these compounds in mediating learning and memory.

- Understanding the molecular mechanisms of cognitive improvement by RAS inhibitors will help in better understanding of their beneficial effect and bridging the existing research gaps.

- The true test of the therapeutic potential of any drug is a clinical trial. Therefore careful monitoring of cognitive performance in patients undergoing therapy with these drugs may need to be undertaken.