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Stephen Todd, Bernadette Mcguinness, a Peter Passmore

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Prevention of dementia by ACE inhibitors and angiotensin receptor blockers – potential but not proven

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Complete List of Authors:	Todd, Stephen; The Queen's University of Belfast, Ageing Group, Centre for Public Health McGuinness, Bernadette; The Queen's University of Belfast, Ageing Group, Centre for Public Health Passmore, A Peter; The Queen's University of Belfast, Ageing Group, Centre for Public Health
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3 Prevention of dementia by ACE inhibitors and angiotensin receptor blockers –
4 potential but not proven
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7 Stephen Todd, Bernadette McGuinness and A. Peter Passmore
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10 Ageing Group
11 Centre for Public Health
12 School of Medicine, Dentistry and Biomedical Sciences
13 The Queen's University of Belfast
14
15

16
17 Corresponding author
18

19 Stephen Todd
20 Ageing Group
21 Centre for Public Health
22 School of Medicine, Dentistry and Biomedical Sciences
23 The Queen's University of Belfast
24 Whitla Medical Building
25 97 Lisburn Road
26 Belfast
27 BT9 7BL, UK
28 s.todd@qub.ac.uk
29 Telephone: +442890972206
30 Facsimile: +442890975870
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37 Disclosures
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3 Dementia currently exacts a substantial economic burden on societies, health and
4 social care systems, and carers in addition to the devastating personal and
5 emotional cost to patients and families [1,2]. This burden is predicted to increase
6 substantially in the coming decades and is the major public health issue of this
7 century [1]. Currently available therapies are symptomatic only [3], with little or no
8 prospect of disease-modifying treatments entering routine clinical use in the short to
9 medium term. Strategies to prevent or delay the onset of dementia or retard its'
10 progression are, therefore, urgently required and will be of extreme importance to
11 individuals and societies. Currently available medications that could achieve these
12 goals would have many advantages – potential for immediate use; established safety
13 profile; familiarity to clinicians; relatively low cost giving favourable cost-effectiveness
14 breakdown.

34 Cardiovascular risk factors and dementia

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38 Recent reports have highlighted that a number of common cardiovascular risk
39 factors are associated with both Alzheimer's disease (AD) and vascular dementia
40 (VaD), the two most prevalent forms of dementia [4,5]. Additionally, *post mortem*
41 studies have demonstrated that the characteristic neuropathological changes of both
42 AD (senile plaques and neurofibrillary tangles) and VaD (subcortical/white matter
43 ischaemia) are highly prevalent in the brains of normal individuals as well as those
44 with AD, VaD, and other forms of dementia [6-8].

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48 From this and earlier work, the hypothesis has arisen that treatment of these
49 common cardiovascular risk factors, in particular hypertension and
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3 hypercholesterolaemia, will result in a reduction in the incidence and/or progression
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5 of dementia. Our group has performed systematic reviews and meta-analyses of
6
7 blood pressure lowering therapies [9] and 3-hydroxy-3-methylglutaryl coenzyme A
8
9 reductase inhibitor (statin) treatment [10] for the prevention of dementia and/or
10
11 cognitive impairment. At present, there is no evidence from randomised clinical trials
12
13 (RCTs) that treatment of either hypertension or hypercholesterolaemia reduces the
14
15 incidence of dementia [9,10]. However, we found several limitations in the literature.
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17 In the blood pressure lowering systematic review [9], significant bias may have been
18
19 introduced by the number of participants lost to follow up, with differential loss
20
21 between active treatment and placebo groups, and the large proportions of placebo
22
23 allocated participants receiving active treatment in the included RCTs. The primary
24
25 outcomes in the included studies were cardiovascular and the studies stopped when
26
27 significant benefits in these primary outcomes were found. Dementia or cognitive
28
29 impairment were secondary outcomes and the assessments used, the duration of
30
31 the trials, and the number of participants randomised may have been insufficient to
32
33 have detected true significance for these outcomes. In the statin prevention
34
35 systematic review [10], only two studies met the inclusion criteria and, again,
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37 cognition was a secondary or tertiary outcome. There was a low rate of incident
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39 dementia in both placebo and active treatment groups.
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51 Do ACE inhibitors and angiotensin type 2 receptor blockers reduce incidence or
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53 progression of dementia?
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57 Two analyses from prospective cohort studies have been reported recently that add
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59 further data to the debate on treatment of hypertension for benefits on cognition [11,
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3 12]. Sink and colleagues [11] examined data from participants of the Cognition
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12]. Sink and colleagues [11] examined data from participants of the Cognition
substudy of the Cardiovascular Health Study [13] on the effect of ACEI use on
cognitive decline. ACEIs were classified into those that crossed the BBB (centrally
active) and those that did not (non-centrally active) using data mainly from animal
studies [11]. The majority of the 1054 participants in the study were female (64%)
and white (76%), with a mean age of 75 years. ACEIs were not associated with a
reduction in the risk of dementia when compared as a class to other anti-
hypertensive drug classes (adjusted HR 1.01; 95% CI 0.87-1.18). However, centrally
active ACEIs were associated with a 65% reduction in cognitive decline, as
measured by the Modified Mini-Mental State Examination (3MSE) [14], per year of
drug exposure as compared to other anti-hypertensive medications (p=0.01). Non-
centrally active ACEIs were associated with a 73% increased risk of dementia over
three years, compared with other anti-hypertensive agents.

The brain, as with most organs, has a paracrine renin-angiotensin system (RAS). In
brain, RAS has specific local effects, including on memory, independent of the
systemic circulatory RAS, unlike other organs such as the heart or kidney [15].
Preliminary data suggest possible effects of drugs acting on RAS on cognition
beyond blood pressure (BP) control. ACE activity is increased in AD *post mortem*
brain and correlates with amyloid plaque load and with AD severity (reviewed in
[16]). Some, but not all, animal studies show alteration in amyloid pathology and
cognitive performance with RAS active medications (reviewed in [16]). ACE
degrades amyloid- β ($A\beta$) peptide, the precursor of plaques, in the brain and captopril
caused an increase in the neurotoxic $A\beta_{42}$ in one mouse model [17]. Therefore, will
long term ACEI therapy have detrimental effects on cognition? Various mouse

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3 models treated with ARBs have been associated with reduced Alzheimer's
4 neuropathology and improved performance on tests of learning and memory
5 [16,18,19]. However, it may not be appropriate to extrapolate animal models to
6 humans. Other small observational studies have also reported reduced progression
7 of mild cognitive impairment to AD [20] and reduced incidence of AD [21]. One small
8 RCT has suggested that centrally active ACEIs slow cognitive decline in AD more
9 than non-centrally active ACEIs or calcium channel blockers [22].

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22 Li and colleagues reported that ARBs were associated with a reduction in the
23 incidence and progression of dementia and AD compared with the ACEI lisinopril
24 and with "cardiovascular comparators" [12]. Of note, Li classified lisinopril as non-
25 centrally active, whereas in Sink's study lisinopril was classified as centrally active. Li
26 *et al.* based their classification on the hydrophilicity of lisinopril [23]. However, this
27 report references an animal study showing prolonged cerebrospinal fluid ACE
28 inhibitory activity by lisinopril [24], suggesting a possible peptide carrier at the BBB.
29 Sink classified central activity or non-activity on the basis of this earlier study [11].
30 The summary of product characteristics for lisinopril states "studies in rats indicate
31 lisinopril crosses the BBB poorly". The cohort was predominantly male (98%) with a
32 mean age of 74 years. Ethnicity was unknown for most subjects. There are several
33 limitations of this study. Firstly, the three groups are not comparable as there are
34 significant differences in morbidity profiles and mean BP and small differences in
35 ethnicity. All of these impacts on the risk or recognition of dementia. The
36 "cardiovascular comparator" group had lower rates of hypertension and diabetes and
37 higher rates of cardiovascular disease and stroke than the ARB and lisinopril groups.
38 Mean BP was 3/2mmHg lower in the "cardiovascular comparator" group. Low BP in
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3 late-life is associated with dementia and AD [4]. The level of absolute BP reduction
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5 rather than the agent(s) used is considered paramount in reduction of cardiovascular
6
7 mortality and morbidity. Secondly, the prevalence of use of other cardiovascular
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9 medications, such as anti-platelet or other anti-hypertensive agents, across the three
10
11 groups was not reported. Statins were specifically excluded from the “cardiovascular
12
13 comparator” group, with no rationale provided. The corresponding author had
14
15 previously reported a similar large association between use of statins and decreased
16
17 prevalence of AD [25]. However, subsequent RCTs have not shown a beneficial
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19 effect of statins on the prevention of dementia [10]. The progression outcome
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21 (nursing home admission) was primarily driven by reduction in stroke in the ARB
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23 group. Modification of risk factors other than BP by use of other agents may have
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25 contributed to this. However, in a RCT of an ACEI and thiazide diuretic regimen,
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27 reduction in stroke recurrence was associated with reduced dementia incidence [26].
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29 Finally, the clinical plausibility of such large reductions in the incidence and
30
31 progression of dementia and AD in a late-life population with relatively short follow
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33 up was not considered. As noted earlier, AD and vascular neuropathological
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35 changes are highly prevalent in this age-group [7] and have been present for many
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37 years before incident dementia becomes symptomatic and is diagnosed.
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48 Vascular risk factor interventions in dementia

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53 There are few interventional studies of vascular risk factor modification, either singly
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55 or in combination, in AD. Observational studies suggested cognition declined less on
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57 statin treatment [27] and function declined less on statin and β -blocker treatment
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3 [28]. However, RCTs have not shown benefit of statins on progression of cognition in
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5 AD.
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10 An observational study reported that treatment of vascular risk factors was
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12 associated with slower cognitive decline in patients with AD and no CVD than no
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14 treatment [29]. One recent small RCT failed to show a benefit of intensive vascular
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16 risk factor modification over usual care in slowing dementia progression in subjects
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18 with AD and vascular lesions on neuroimaging [30]. It may be that this stage of the
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20 disease process with established neuropathology is too late to initiate these
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22 treatments. However, although BP was reduced in both intensive and usual care
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24 groups, the difference was not significant [30]. It is possible that lowering BP and
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26 cholesterol in AD may be harmful as blood pressure falls in older people with AD [4]
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28 and cholesterol may be lower in AD [5]. A trial is ongoing to establish if a similar
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30 regimen is of benefit in reducing dementia incidence in elderly people with vascular
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32 risk factors (ISRCTN29711771) [31].
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41 Conclusions

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46 Given the current lack of reliable RCT evidence and these interesting but limited
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48 retrospective, observational studies, several questions remain to be answered: does
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50 treatment of hypertension in mid-life result in reduced risk of dementia or cognitive
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52 decline in late-life? Does treatment of hypertension in late-life result in reduced
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54 incidence and/or progression of dementia? If so, is one anti-hypertensive class, or
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56 sub-group that crosses the BBB, associated with these better cognitive outcomes?
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58 Are certain anti-hypertensives, such as ACEIs discussed previously [16], associated
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3 with worse cognitive outcomes? Does addressing the overall cardiovascular risk with
4 lifestyle interventions, antiplatelet and lipid lowering therapies, in addition to
5
6 antihypertensives, provide additional benefit in reducing dementia incidence or
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8 progression? As has been suggested previously by other commentators [16,32], the
9
10 recent reports highlight that well designed RCTs, adequately powered and of
11
12 sufficient duration to answer these questions, with appropriate primary outcomes
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14 which assess dementia (and subtype) incidence and progression are urgently
15
16 required. The use of effective, inexpensive, currently available therapies to reduce
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18 the considerable burden from dementia would be of major benefit to older individuals
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20 and their carers, health and social systems, and economies not only in the
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22 developed world but also the developing world [33].
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Author Contributions

ST: drafting article, critical revision of article, approval of article

BMcG: critical revision of article, approval of article

APP: critical revision of article, approval of article

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