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Clinical Study

Effect of Telmisartan on Cerebral and Systemic Haemodynamics in Patients with Recent Ischaemic Stroke: A Randomised Controlled Trial

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High blood pressure (BP) is common in acute stroke and is independently associated with a poor outcome. Lowering BP might improve outcome if cerebral blood flow (CBF) is unaffected in the presence of dysfunctional autoregulation. We investigated the effect of telmisartan on systemic and cerebral haemodynamics in patients with recent stroke. Patients with ischaemic stroke (<5 days) were randomised to 90 days of telmisartan (80 mg) or placebo. CBF (primary outcome) was measured using xenon CT at baseline and 4 hours. BP and transcranial doppler (TCD) were performed at baseline, 4 hours after-treatment, and on days 4, 7, and 90. Cerebral perfusion pressure and zero filling pressure (ZFP) were calculated. Of a planned 24 patients, 17 were recruited. Telmisartan significantly accentuated the fall in systolic and diastolic BP over 90 days (treatment-time interaction $p = 0.047$, $p = 0.003$, resp.) but did not alter BP at 4 hours after treatment (171/99 versus 167/87 mmHg), CBF, or CBF velocity. ZFP was significantly lower in the treatment group ($p = 0.018$). Impairment at 7 days and dependency at 90 days did not differ between the groups. In this underpowered study, telmisartan did not significantly alter BP or CBF after the first dose. Telmisartan reduced BP over the subsequent 90 days and significantly lowered ZFP. This trial is registered with ISRCTN 41456162.

1. Introduction

High blood pressure (BP) is common and associated independently with a poor outcome in patients with acute stroke [1–3]. However, there are no definitive data guiding the management of high BP. Individual small studies of BP modifying agents in acute stroke have indicated potential efficacy [4–6] or harm [7, 8]. A metaregression analysis of these and other trials suggested that systolic BP reductions in the order of 10–15 mmHg reduction were associated with a trend to reduced death at the end of trial, although the confidence intervals were wide and compatible with benefit or harm [9]; more extreme BP lowering or any form of BP elevation was associated with harm [3, 9]. The recently published large SCAST trial showed that candesartan only modestly lowered BP and had no beneficial effect on dependency or further vascular events [10]. Further large trials of BP lowering in acute stroke are underway including ENOS and INTERACT-2 [11]. However, since antihypertensive agents vary in their mode of action and their potential effects on cerebral blood flow, trials of individual agents may not be generalisable across all antihypertensive agents.

Cerebral autoregulation is dysfunctional in acute stroke [12] and BP lowering could worsen outcome through reducing regional cerebral blood flow (CBF). There are several small trials that have examined the effect of lowering BP with various antihypertensive agents and a meta-analysis of these suggests that lowering BP may not alter CBF adversely [13].

Importantly, cerebral perfusion is dependent on several factors: the "driving" arterial pressure and the downstream

zero-flow pressure (ZFP) which comprises intracerebral pressure (ICP) and central venous pressure. Cerebral perfusion pressure (CPP) is a derived measurement and is equivalent to the mathematical difference between mean arterial pressure (MAP) and ZFP. Some vasoactive drugs may reduce ZFP by inducing cerebral venodilatation, thereby increasing CPP [14, 15].

Telmisartan is a long acting angiotensin receptor antagonist licensed for the treatment of essential hypertension. It was assessed in the PRoFESS stroke secondary prevention megatrial although treatment was not associated with reduced stroke recurrence [16]. In this study, we examined the effect of telmisartan on BP, CBF, CPP, ZFP, and arterial compliance in patients with recent ischaemic stroke.

2. Methods

We performed a prospective, randomized controlled, double-blind, and blinded-outcome trial (ISRCTN 41456162). Approval was obtained from the Leicestershire, Northamptonshire and Rutland Ethics Committee 1 (approved 6th December 2006, Reference 06/Q2501/228) and the UK Medicines and Healthcare products Regulatory Agency (approved 20th November 2006, Eudract number 2006-005082-19). Patients gave written informed consent or, where they lacked capacity, proxy consent was obtained from next of kin. The study conformed to the Declaration of Helsinki and International Conference on Harmonisation guidelines and was performed under Good Clinical Practice. Enrolment took place between July 2007 and December 2009. The study protocol as approved by the ethics committee is available as a supporting document with this paper.

2.1. Subjects. Patients were recruited from inpatient stroke services at Nottingham City Hospital, and all data was collected here or in the patients' home during the follow-up period. Adult patients with CT confirmed or suspected supratentorial ischaemic stroke where CBF scanning could be completed within 5 days of ictus were eligible. Patients had to have an elevated systolic BP (>140 mmHg) and were excluded if they had a contraindication to telmisartan or xenon CT scanning, or had no enteral access. Patients had prestroke antihypertensive medication stopped following enrolment and during the course of CBF scanning. Imaging of the brain and intra- and extracranial vessels was not required before entry into the trial, but if this information was available patients with intracerebral haemorrhage or severe or multiple vessel stenosis were excluded. Enrolment was carried out by GMS and SA. Blinded followup was carried out by GMS, SA, FH, and TE.

2.2. Randomisation. Patients were randomised (PB) using computerised minimisation on the following variables: age (≤65, >65 years), sex (female, male), baseline systolic BP (≤160, >160 mmHg), baseline Scandinavian Stroke Scale (SSS, ≥40, <40), time to first xenon CT scan (≥48, <48 hours), and cortical features according to OCSP syndromic criteria. Randomisation and minimisation were carried out by PB who had no contact with the trial patients or other trial data prior to unblinding. The sequence was generated by the trial pharmacist.

2.3. Intervention. Patients were treated with telmisartan (80 mg daily) versus matching placebo in a ratio of 2 : 1 and given for 90 days administered orally or via nasogastric tube. All trial participants, their families, and trial staff with the exception of PB were blinded to treatment allocation until the close of the trial. Times shown in the results ("hours" and "days") refer to time from treatment, not randomisation or stroke onset.

2.4. Outcomes. The primary outcome was change in hemispheric CBF on the affected brain side measured by xenon CT. Secondary outcomes included effects on other CBF measures, BP, cerebral blood flow velocity, calculated measures of CPP and ZFP, and clinical dependency and impairment.

2.5. Cerebral Blood Flow. Quantitative regional CBF was measured using the stable xenon CT method (Diversified Diagnostic Products XeCT system 2) [17, 18]. A baseline CT scan was performed and the infarct area identified. Four 10 mm thick slices encompassing the infarct (and surrounding brain if the infarct was seen on less than 4 slices) were then rescanned with the administration of 28% xenon gas to determine baseline absolute CBF. Patients then received telmisartan 80 mg or matching placebo and were rescanned using an identical technique 4 hours after administration.

CBF was calculated on a PC using XeCT software in an identical manner for pre and post treatment scans. Images with excessive movement artefact were discarded. Analyses (by GMS) were blinded to treatment and concentrated on the slice with the largest visible area of stroke lesion.

CBF measurements in mLs/min/100 g were calculated for the entire brain slice selected (global CBF), for the ipsilateral and contralateral hemispheres (hemispheric CBF), and for preset cortical regions supplied by the anterior, middle, and posterior cerebral arteries. Blood flow within the infarct area was further characterised using a pixel based analysis by identifying a region of interest (ROI) around the infarct and surrounding normal brain tissue. A CBF filter was then used to determine the number of pixels within the ROI matching prespecified CBF values for "core" (0 to 9 mL/min/100 g), "penumbra" (10 to 19 mL/min per 100 g), and "oligemia" (20 to 36 mL/min per 100 g) [19–21]. ROIs were matched for site on pre- and posttreatment scans.

2.6. Blood Pressure. BP was measured using an Omron HEM-705CP (Omron, 705IT, Kyoto, Japan) semiautomatic sphygmomanometer with patients supine or sitting; measurements were taken in the unaffected arm and done in duplicate with the average of the two readings recorded in the database. MAP was calculated as

$$\mathrm{MAP} = \mathrm{DBP} + \frac{(\mathrm{SBP} - \mathrm{DBP})}{3}. \quad (1)$$

2.7. Central Haemodynamics. Central haemodynamics were recorded using a SphygmoCor (AtCor Medical, Sydney, Australia) device. A probe was place on the radial pulse of the unaffected arm and pulse wave analysis allowed indirect measurement of central BP, augmentation index (a measure of arterial stiffness) [22], and Buckberg index (a ratio of systole to diastole thereby assessing cardiac perfusion).

2.8. Transcranial Doppler. Transcranial doppler (TCD) studies were performed using a Companion III (VIASYS, Hong Kong) TCD machine. The middle cerebral arteries in the ipsilateral and contralateral hemispheres were identified and measurements were made at the observed peak systolic flow velocity (FV); measurements included systolic, mean, and diastolic flow velocity and pulsatility index.

CPP and ZFP were subsequently calculated for each time point using the following formulae [14, 15]:

$$\text{CPP} = \frac{\text{mean FV}}{(\text{mean FV} - \text{diastolic FV}) \times (\text{MAP} - \text{DBP})}$$
$$\text{ZFP} = \text{MAP} - \text{CPP}. \quad (2)$$

2.9. Functional Outcome. Clinical assessments were performed at entry into the trial (baseline), 4 hours after administration of telmisartan/placebo, and on days 4, 7, and 90. SSS (severity/impairment) was recorded at each time point, and the modified Rankin Scale (mRS, functional outcome) was determined at day 90.

2.10. Statistical Analysis. The primary outcome of the trial was the change in hemispheric CBF on the effected side. A sample size of 24 was required assuming a difference (standard deviation) in CBF of 10 (7) mL/min/100 gm [18], significance of $p = 0.05$, power of $1 - \beta = 0.90$, and a treatment ratio of 2 : 1. Allowing for inclusion of some patients with intracerebral haemorrhage (where no previous scan had been performed) and losses from patients who did not have a second xenon CT scan performed, it was estimated that up to 34 patients might need to be enrolled.

Data were entered and analysed by intention-to-treat using SPSS (Apple Mac version 16, SPSS Inc.). All of the comparisons of haemodynamic and BP data between the treatment groups were analysed using linear regression with adjustment for baseline values using ANCOVA. Measurements at multiple time points were analysed using repeated measures ANOVA and t-test comparison of area under the curve calculations. Significance was set at $p \leq 0.05$.

3. Results

3.1. Subjects. Patients were recruited between July 2007 and October 2009. Of the required 24 ischaemic stroke patients, 19 consented to join the trial, were randomized, and had baseline measurements taken (Figure 1). Recruitment was limited by the reluctance of many potential patients to have two xenon CT scans. The study was closed in January 2010 with a time-limited grant preventing continuation of the trial until recruitment targets were achieved. 12 patients were randomised to telmisartan and seven to placebo and their baseline characteristics are shown in Table 1. The groups were well balanced at baseline and all patients had a stroke lesion seen on CT scan. Following enrolment, two patients were withdrawn from the trial before they had received study medication—one died, and the other was withdrawn as scanning showed watershed infarctions and multiple occlusion of cerebral arteries. Hence, 17 patients (telmisartan 10, placebo 7) received medication and all took this for at least 4 days. One patient had study drug withdrawn (for deteriorating renal function) and subsequently died before the day 90 assessment (placebo), and three others had study drug (all telmisartan) withdrawn, two for deteriorating renal function, and one because of low BP. Fifteen patients successfully completed the xenon CT protocol; one patient became too unwell to scan, and another failed to tolerate the second scan. Table 2 shows the baseline haemodynamics for the treatment groups. Although there were no significant differences between the groups, SBP measured immediately before the first prexenon CT scan was less well matched than that measured at baseline after consent.

3.2. Cerebral Blood Flow. Table 3 summarises the effect of treatment on cerebral haemodynamics. There was no significant effect of telmisartan on hemispheric CBF (primary outcome), other measures of CBF, or CBF velocity measured by TCD. Figure 2 is a scatter plot showing individual patient data relating change in SBP over 4 hours with change in MCA territory CBF; there was no relationship between the two variables.

3.3. Blood Pressure. Although well matched at randomisation, patients in the telmisartan group had a mean SBP 10.4 mmHg lower than the control group at the baseline measurement, immediately prior to CT scanning. BP fell during the trial period in both treatment groups (Figure 3). At four hours after-treatment, BP rose in the placebo group as compared with baseline and fell slightly in the telmisartan group; however, the difference in BP between the treatment groups at this time point was not significantly different: systolic BP—11.6 mmHg (95% CI—39.9, +16.6, $p = 0.39$), diastolic BP—12.6 mmHg (95% CI—26.6, +1.4, $p = 0.075$). Over the 90 days, the interaction between telmisartan and time was significant for both systolic ($p = 0.047$) and diastolic ($p = 0.004$) BP (repeated measures ANOVA). Telmisartan lowered DBP ($p = 0.043$) but not SBP ($p = 0.18$) (comparison of area under the curve).

3.4. Central Haemodynamics. There was no significant difference between the treatment groups with respect to central SBP, DBP, augmentation index, or Buckberg index (Table 3).

3.5. Derived Measures. There was no treatment effect or treatment-time interaction for CPP. Although telmisartan did not alter ZFP at four hours, ZFP was lower over the 90 days

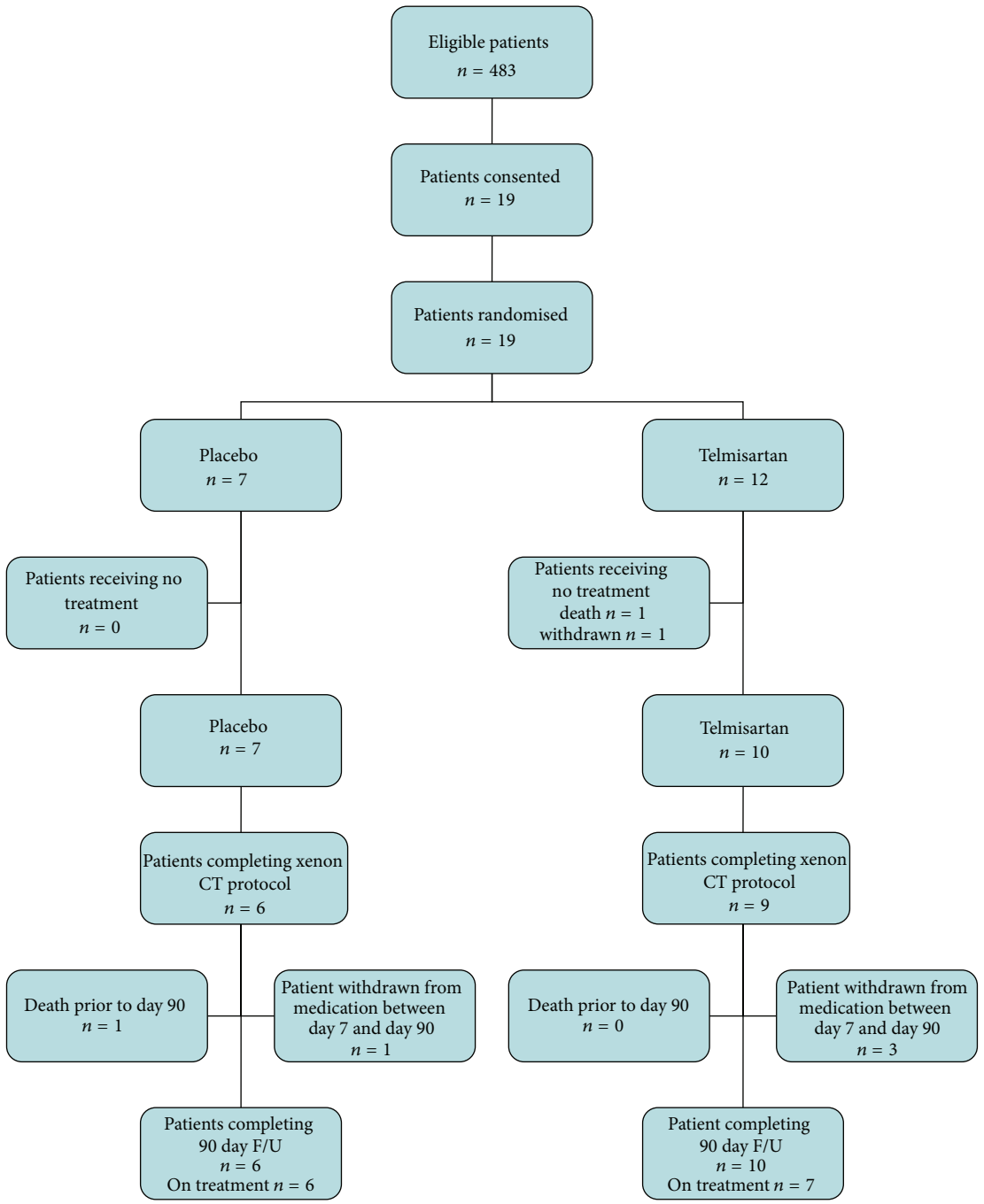

Figure 1: Flow diagram of patient participation in the trial.

of treatment (area under the curve comparison, $p = 0.018$) (Figure 4).

3.6. Functional Outcome. Neurological impairment did not differ between the treatment groups at either day 7 or day 90 (Table 4). Similarly, there was no difference in functional outcome at day 90. There were three serious adverse events in two patients in the trial (both patients died); one patient died before he received study medication (and therefore was excluded from analysis), and the other was off medication for two months prior to death following a myocardial infarction.

4. Discussion

This trial aimed to assess the effect of telmisartan, an ARA licensed for the treatment of hypertension, on CBF in patients with very recent stroke. An implicit assumption underlying the trial was that telmisartan would lower blood pressure by 4 hours after the first dose. However, a maximum licensed dose of 80 mg telmisartan did not significantly reduce BP at this time point; hence the absence of any effect of telmisartan on any measure of CBF or CBF velocity is not surprising. As a result, the study cannot answer the question of whether BP

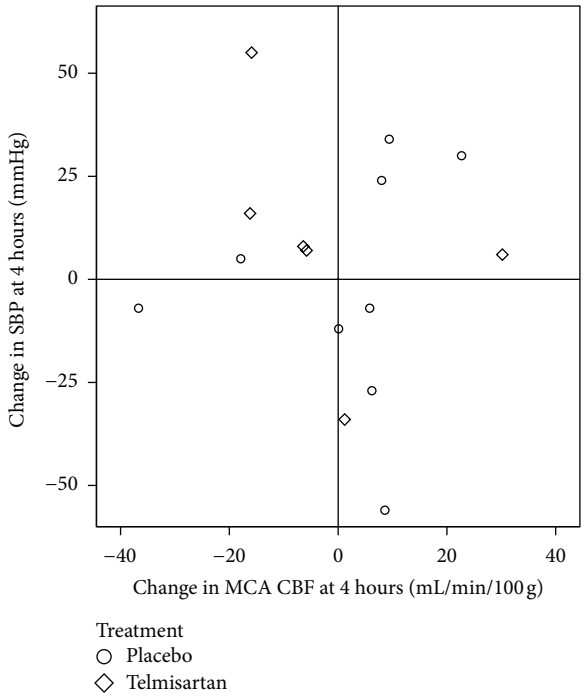

Figure 2: Scatter plot of change in ipsilateral MCA cerebral blood flow against change in systolic blood pressure, four hours after first dose study drug.

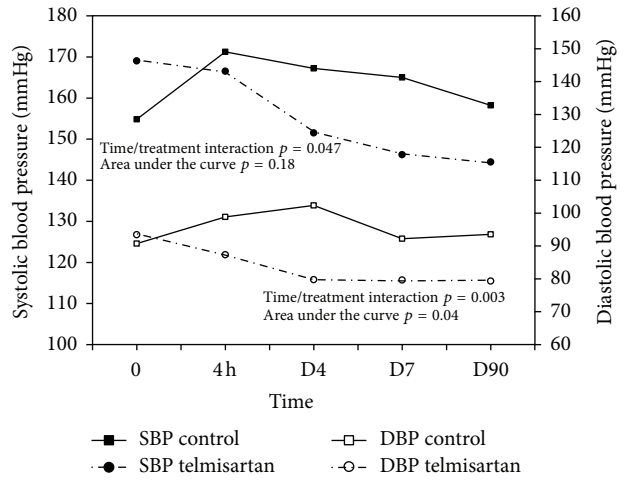

Figure 3: The effect of telmisartan on systolic and diastolic blood pressure over time.

lowering with telmisartan in recent stroke effectively alters BP and subsequently cannot assess the effect of BP lowering on CBF and other haemodynamic measures. This contrasts with our previous work with transdermal glyceryl trinitrate which did lower BP acutely without altering CBF [18]. It is noted that at four hours BP had risen in the placebo but not telmisartan arm, perhaps reflecting a stress response to CT scanning; a similar response occurred in the control group of the GTN trial [18]. It is of note that, due to the small sample size, confidence intervals are wide and the study is compatible with both large positive and negative effects.

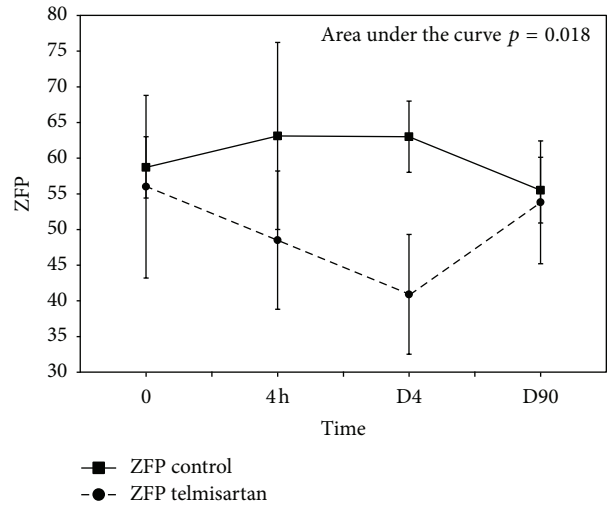

Figure 4: The effect of telmisartan on zero filling pressure (ZFP) over time.

Table 1: Baseline characteristics by treatment group. Mean (standard deviation) or frequency (%).

Variable	Telmisartan	Placebo
Subjects	12	7
Age (years)	71.9 (12.9)	68.3 (15.6)
Sex (male)	10 (83)	4 (57)
Systolic BP (at randomisation, mmHg)	165.7 (12.5)	166.0 (16.7)
Previous hypertension	6 (50)	5 (71)
Previous stroke	1 (8)	1 (14)
Previous diabetes mellitus	0 (0)	2 (29)
Previous atrial fibrillation	3 (25)	1 (14)
Previous ischaemic heart disease	2 (17)	2 (29)
Previous high cholesterol	4 (33)	4 (57)
Smoking status		
Current	2 (17)	2 (29)
Past	5 (42)	5 (71)
Never	5 (42)	0 (0)
Time to baseline scan (hours)	57.9 (20.1)	67.8 (21.5)
Scandinavian Stroke Scale (/58)	48.1 (11.8)	47.9 (8.1)
Cortical syndrome (OCSP)	7 (59)	1 (14)
Prestroke antihypertensive treatment	5 (42)	4 (57)
Diuretic	1 (8)	2 (22)
Beta blocker	5 (42)	1 (11)
Alpha-blocker	0	2 (22)
Angiotensin receptor blocker	2 (17)	0
ACE inhibitor	0	2 (22)
Calcium channel antagonist	1 (8)	2 (22)
Other	0	0

OCSP: Oxford community stroke project.

Over the 90-day treatment period, telmisartan did reduce BP although the effect appeared to be less at 90 days

Table 2: Baseline haemodynamic measures. Mean (standard deviation) number of subjects.

Characteristic	Telmisartan	Placebo
Blood pressure (mmHg) $n = 12$ versus 7		
Systolic BP	168.1 (21.3)	157.7 (21.4)
Mean arterial BP	117.4 (14.6)	113.1 (14.2)
Diastolic BP	91.6 (16.8)	90.9 (12.4)
Heart rate (bpm)	69.6 (15.8)	74.6 (14.6)
Cerebral blood flow, ipsilateral hemisphere (mL/min/100 g) $n = 9$ versus 7		
Global	42.2 (13.5)	47.3 (20.9)
Hemispheric	42.1 (14.3)	45.7 (19.7)
Anterior cerebral artery	42.0 (13.2)	45.4 (25.7)
Middle cerebral artery	48.1 (23.3)	45.5 (20.3)
Posterior cerebral artery	44.6 (18.9)	47.8 (24.9)
Cerebral blood flow, contralateral hemisphere (mL/min/100 g) $n = 9$ versus 7		
Global		
Hemispheric	42.6 (12.8)	50.1 (22.8)
Anterior cerebral artery	48.2 (16.5)	49.2 (27.1)
Middle cerebral artery	49.1 (18.4)	53.3 (23.8)
Posterior cerebral artery	42.4 (12.6)	44.8 (23.9)
Lesion area (pixels) $n = 9$ versus 7		
Total	1102 (884)	1082 (688)
Oligaemia	240 (146)	237 (176)
Penumbra	200 (302)	162 (190)
Core	268 (511)	264 (561)
Transcranial doppler measures, ipsilateral $n = 9$ versus 5		
Systolic cerebral blood flow velocity (cm/s)	65.9 (20.1)	51.2 (16.3)
Pulsatility index	1.06 (0.20)	1.08 (0.21)
Cerebral perfusion pressure	66.8 (14.2)	58.6 (13.6)
Zero filling pressure	48.3 (16.3)	58.1 (3.2)

reflecting the introduction of additional antihypertensives for secondary prevention in the placebo group and discontinuation of treatment in the telmisartan group. No effects of telmisartan on central BP were present.

Using repeated cerebral haemodynamic measurements, telmisartan lowered ZFP over the 90 days of the trial. ZFP is a measure of the downstream pressure providing resistance to the outflow of blood from the brain and is comprised of a combination of ICP and venous pressure. Telmisartan did not reduce CPP, presumably through its effect lowering MAP, so the reduced ZFP may indicate that BP can be safely lowered without compromising cerebral perfusion.

The explanation for the lack of first dose effect is unclear and there may be several contributing factors. First, oral telmisartan has a time to peak plasma concentration of ~1 hour and time to maximum effect of ~2 hours in haemodynamic studies on healthy volunteers or hypertensive patients [23, 24]; there are no data in patients with recent stroke. Assessment at 4 hours may not have been optimal in our study population. Second, the imbalance in BP between the groups at baseline may have masked some of the BP difference given the rise in BP in the control group at 4 hours. Importantly, as the study was underpowered, we cannot exclude that the lack of effect was due to type II error; that is, the study was smaller than intended (19 patients rather than 24), although it was of similar size to our GTN trial where BP lowering was demonstrated after one dose [18]. This trial had difficulty recruiting because many potential participants (or their relatives if proxy consent was required) were unwilling to undergo xenon CT scanning. Limited size has been a feature of previous studies of CBF in acute/subacute stroke, as summarised in a meta-analysis of these [13].

As well as the lack of a significant treatment effect, there are several other important caveats to discuss about this trial. First, patients were recruited if scanning could be completed within 5 days of stroke onset and had a mean time to enrolment of 68 (sd 19) hours. Ideally, patients would have been assessed rapidly after stroke onset during the hyperacute and early acute phase, although the recruitment problems would have been exacerbated significantly. Second, all patients with ischaemic stroke were eligible so a mix of patients with lacunar, large vessel, or cardioembolic stroke were included. Lowering BP after ischaemic stroke may have differing effects in different stroke subtypes; however, there was no significant difference in subtype distributions between treatment groups in this study. Third, three of 10 patients receiving telmisartan were withdrawn from treatment between day 7 and 90 due to potential adverse reactions (deteriorating renal function and hypotension), which limits the on treatment data available for day 90 assessment. Last, while the SD for CBF in our sample size calculation was taken from our earlier study [18], it was far below the variation seen here.

This trial was conceived and funded at a time when ARAs were a hopeful therapeutic intervention in stroke. The ACCESS trial had demonstrated that oral candesartan given in the subacute period reduced recurrent vascular events (secondary outcome) although there was no effect on the primary outcome (Barthel index) [25] and other large trials were underway and have now reported. Following the ACCESS trial, a further and much larger trial, SCAST, randomised patients to oral candesartan or placebo within 30 hours of stroke onset [10]. As here, SCAST found that the first dose of candesartan had a very modest effect on BP over the first day (3.3/1.3 mmHg). Furthermore, although SCAST was neutral overall, treatment with candesartan was associated with a strong trend to worse functional outcome at 6 months [10]. In addition to their BP lowering properties, it had been suggested that ARAs may have neuroprotective mechanisms in stroke mediated via its selective action on the AT1 rather than AT2 receptors and had shown potential in animal models [26, 27]. Telmisartan was considered a particularly interesting agent due to its high affinity for the AT1 receptor [28] and it long plasma half-life [29]. The PRoFESS megatrial found that telmisartan did not reduce stroke recurrnce over

Table 3: Effect of telmisartan on haemodynamic measures at four hours.

Measurement	Control (n)	Telmisartan (n)	Control (mean/sd)	Telmisartan (mean/sd)	Difference (t, 95% CI)	p value
CBF, mL/min/100 g						
Global	6	9	41.4 (10.0)	46.3 (10.1)	−1.2 (−16.9, 4.6)	0.24
Ipsilateral hemispheric	6	9	38.9 (10.4)	45.4 (10.6)	−1.5 (−17.8, 3.1)	0.15
ACA	6	9	48.6 (16.2)	50.4 (10.1)	−0.3 (−16.5, 12.0)	0.74
MCA	6	9	40.2 (11.9)	48.7 (10.7)	−1.4 (−17.2, 3.7)	0.18
PCA	6	9	39.9 (13.1)	53.0 (27.2)	−1.5 (−37.8, 6.4)	0.15
CBF, mL/min/100 g						
Contralateral hemispheric	6	9	42.7 (9.4)	47.2 (10.2)	−1.1 (−17.4, 5.9)	0.30
ACA	6	9	56.0 (21.4)	55.5 (11.0)	0.03 (−18.6, 19.1)	0.99
MCA	6	9	46.5 (10.2)	49.5 (12.7)	−0.7 (−16.9, 8.8)	0.51
PCA	6	9	41.8 (12.6)	51.2 (15.3)	−1.3 (27.0, 6.7)	0.21
Lesion area, pixels	6	9	1171 (690)	1114 (905)	−1 (−53, 22)	0.38
Oligaemia	6	9	315 (184)	273 (183)	0 (−141, 193)	0.74
Penumbra	6	9	207 (191)	154 (183)	2 (−21, 146)	0.13
Core	6	9	206 (290)	139 (213)	1 (−68, 171)	0.36
TCD ipsilateral						
Systolic CBFv (cm/s)	4	6	61.0 (13.0)	80.5 (24.0)	−0.8 (−33.5, 16.5)	0.45
CPP	4	6	61.0 (10.8)	56.6 (13.2)	0.5 (−16.6, 26.3)	0.61
ZFP	4	6	56.8 (16.5)	48.5 (9.7)	0.9 (−11.8, 26.2)	0.40
Augmentation index	7	9	29.3 (10.3)	28.4 (12.4)	1.1 (−6.0, 17.7)	0.31
Buckberg index	7	9	162.4 (38.3)	161.7 (35.9)	−2.1 (−49.3, 0.8)	0.06

Table 4: The effect of telmisartan on outcome and stroke classification.

Outcome measure	Control (n)	Telmisartan (n)	Control (mean sd/median IQR/%)	Telmisartan (mean sd/median IQR/%)	Unadjusted p-value	Adjusted p-value[#]
Day 7 SSS[a]	7	11	53.7 (4.3)	48.8 (16.9)	0.20	0.07
Day 90 SSS[a]	6	10	54.5 (2.7)	55.9 (3.0)	0.43	0.41
Day 90 mRS[*]	7	11	2 (2, 3)	2 (1, 2)	0.24	0.11
TOAST	7	12				
Large artery	2	7	28.6	58.3	0.35	—
Small vessel	4	3	57.1	25.0		
Cardioembolic	1	2	14.3	16.7		

[a]ANCOVA, [*]ordinal regression (unadjusted), [#]ordinal regression adjusted for age.

2.5 years of followup and did not exhibit neuroprotective properties [16, 30]. A subgroup analysis within PRoFESS focussed on 1,360 patients randomised to oral telmisartan or placebo within 72 hours of stroke onset [31]; there was no significant effect on functional outcome or early recurrence. Taking the results of the current and these earlier trials together, there seems to be little value in pursuing ARAs as a treatment in subacute stroke.

It is possible that the design of these trials was suboptimal. Any neuroprotective benefit of agents, whether mediated via BP lowering or other pathways, is likely to be most beneficial if given in the hyperacute setting. The technical difficulty of hyperacute trials makes investigating this hypothesis difficult but the success of thrombolysis trials [32, 33] suggests it is possible. It also remains to be seen whether the failure of ARAs is applicable to other BP lowering agents. The pilot CHHIPS trial showed a reduction in mortality (a secondary outcome) at 3 months in patients treated with a β-receptor antagonist (labetalol) or ACE-I (lisinopril) within 36 hours of stroke onset. The ongoing ENOS trial [34], assessing the effect of transdermal GTN within 48 hours of stroke onset, will report in 2014.

5. Conclusions

In summary, this small study found that the first dose of telmisartan did not lower BP and had no effect on CBF or other measures of cerebral haemodynamics in patients with recent ischaemic stroke. A lack of statistical power may account for the neutral result. However, over 90 days, patients treated with telmisartan showed a significant reduction in BP and ZFP, a measure of resistance to outflow of blood from the brain.

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