TElmisartan in the management of abDominal aortic aneurYsm

(TEDY)

Protocol Version: 9.1
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STUDY ACKNOWLEDGMENT/CONFIDENTIALITY

By signing this Protocol, the Investigator(s) acknowledges and agrees:

The Protocol contains all necessary details for conducting the study. The Investigator will conduct this study as detailed herein, in compliance with Good Clinical Practice (GCP), The National Statement on Ethical Conduct in Human Research, the Australian Code for Responsible Conduct of Research and the applicable regulatory requirements, and will make every reasonable effort to complete the study within the time designated.

The Protocol and all relevant information on the drug relating to pre-clinical and prior clinical experience will be made available to all physicians, nurses and other personnel who participate in the conducting of this study. The Investigator will discuss this material with them to assure that they are fully informed regarding the drug(s) and the conduct of the study.

The Chief Investigator (or delegate) will have access to any source documents from which Case Report Form information may have been generated. The Case Report Forms and other data pertinent to this study are the sole property of, the Chief Investigator, who may utilise the data in various ways, such as for submission to government regulatory authorities, or in publication of the results of the study.

The conduct and results of this study will be kept confidential. The results of this study may be published. Upon completion of the Study it is the intention of the parties to prepare a joint publication regarding or describing the Study and all the results there from and both parties shall co-operate in this regard. Where it is the intention of the Chief Investigator to file for a patent or other intellectual property right protection, publication may be deferred for up to twelve months from the date of completion of the proposed joint publication to allow the Chief Investigator to make all filings it deems appropriate.

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Contents

1 HYPOTHESIS

Abdominal aortic aneurysm (AAA) is responsible for approximately 1000 deaths per year and is estimated to cost the health economy in excess of $80 million per year to manage in Australia. Early stage AAAs can be readily detected by screening or incidental imaging but currently this is of limited value as no effective medical therapy is available to inhibit AAA progression to a size where aortic rupture is a concern and surgery is therefore required. In a double blind, placebo controlled, randomised trial among participants with 35-49mm AAA, our aims are to investigate the efficacy of telmisartan as a possible treatment for AAA. We hypothesise that among patients with AAAs with an initial diameter of 35-49mm, 40mg of telmisartan administered daily for a 2 year period will reduce AAA expansion by 35% evidenced by:

1. Reduction in average yearly increase in AAA diameter from 2.0±1.7 to 1.5±1.3 mm
2. Reduction in average yearly increase in AAA volume from 6.20±5.90 to 4.65±4.42 cm^3

2 AIMS

2.1 Primary Aim

The primary aim of this study is to investigate if telmisartan reduces AAA growth
Aim 1 will be assessed by investigation of change in maximum AAA diameter on repeat ultrasound

2.2 Secondary Aims

The secondary aims of this study are to investigate how treatment with Telmisartan effects:

1. Changes in maximum orthogonal AAA diameter and total infrarenal aortic volume on CT
2. Circulating biomarkers for AAA progression
3. Health-related quality of life
4. Blood pressure
5. Requirement for AAA surgery

Data from this study will also allow a much more careful analysis than previous of the association of biomarkers and other clinical risk factors with AAA progression.

Aim 2 will be assessed by investigation of the change in serum osteoprotegerin (OPG), osteopontin (OPN), matrix metalloproteinase 9 (MMP-9) and Transforming Growth Factor-Beta one (TGF-β1) and plasma D-dimer on repeat sampling over 2 years. Circulating concentrations of these two biomarkers have been found to be predictive of AAA progression. Previous studies indicate that D-dimer is currently the most reproducible biomarker for AAA [100, 101,106,103, 104]. Furthermore our previous work suggests that OPG is a primary target of both AT1 blockers and PPARγ ligation in inhibiting AAA progression [100,107,108].

Analysis of risk factors will be performed through participant interviews, and assessment of medical records and current medications. Assessment of blood pressure will be performed at 0, 3, 6, 12, 18, 24 months. Quality of life will be assessed by the short form 36 (SF-36) completed at 0, 12 and 24 months, which we have previously validated for use in patients with peripheral artery disease [46]. Requirement for AAA surgery will be determined by the treating Vascular Surgeon.

Other important events monitored will include:

I. AAA rupture
II. Cause of death as reported on the death certificate
III. Myocardial infarction
IV. Stroke
V. Cardiovascular events of clinical importance
VI. Changes in background medication

3 BACKGROUND

3.1 Present Management and Significance of AAA

AAA affects 5% of men and 1% of women greater than 60 years [1,2]. AAA is the 10th most common cause of death in men aged greater than 60 years [2]. In 2004, 471 deaths (5/100,000/yr) and 2,169 hospitalisations (50/100,000/yr) were recorded in New South Wales alone as a result of AAA [3]. The present management options for AAA are either surgical repair (open or endovascular) or follow-up by imaging at intervals (i.e. conservative treatment with no therapeutic intervention). Currently approximately 3000 AAA repairs are performed annually in Australia at a cost of approximately $100 million. In the USA, approximately 50,000 endovascular and open AAA repairs are performed annually at a cost of more than $1000 million [4]. Despite the increasing numbers of elective AAA repairs, approximately 1,500 and 15,000 deaths respectively are attributed to AAA annually in Australia and the USA, illustrating that the problem remains poorly treated [5,6].

In view of the increasing importance of AAA as a cause of mortality, ultrasound screening of at risk individuals has been introduced to detect AAAs in most of the developed world [7]. Such screening of at risk individuals, either on a population basis or as arranged by practitioners selectively usually identifies AAAs of small size, with 90% measuring greater than 50mm [8]. Two large randomised controlled trials have provided evidence that early elective open surgery for AAAs measuring 40-55mm does not reduce mortality [9,10]. Currently a further two trials are examining the value of endovascular repair for 40-54mm AAAs [11,12]. Initial reports from one trial suggest that similar to open repair, endovascular surgery is not beneficial for small AAAs, which is in keeping with the reported need for re-intervention in up to 20% of participants after minimally invasive surgery [13-15]. In summary, surgery does not appear to offer any solution for the increasing number of participants with small AAAs.

3.2 The Urgent Need for an Effective Drug Therapy for Small AAA

It is currently estimated that 100,000 Australians have small AAAs. These patients are treated conservatively, given that surgery has not been shown to be beneficial for AAA less than 5cm and instead are followed by repeated and costly imaging and clinical consultations for extended periods [4,9,10,15-17]. Furthermore, due to continued aortic expansion up to 70% of participants later require surgery in any case [9,10]. There is thus an urgent need to identify medications that can slow aortic destruction.

Such drug therapy could be used in participants with small AAAs to reduce the number later requiring surgery, in those unsuitable for AAA repair and to reduce the need for secondary intervention in those previously treated by surgery [18]. There is presently no evidence that control of atherosclerotic risk factors alone reduces AAA progression. Such treatment is however clearly advisable in these participants in order to reduce cardiovascular events [19]. Only one completed randomised trial has been adequately powered to reliably examine the efficacy of medication in limiting progression of AAA [18,20]. The study demonstrated no benefit from propranolol [20]. Medications shown to slow AAA progression in animal models and small or non-randomised human studies include statins, macrolides, cyclooxygenase inhibitors and other developmental drugs such as c-Jun N-terminal kinase inhibitors [18,21-24].

In order to be successfully investigated in a randomised trial as a drug treatment for AAA, a potential medication requires a number of important characteristics including; evidence to support its benefit, a good safety profile from phase II studies or by virtue of its use for other conditions, a large proportion of individuals with AAAs in whom the medication is not already indicated and likelihood of good compliance. All the medications listed above are limited in at least one of these categories. While statins are promising and well tolerated drugs, they are already indicated and prescribed in the majority of participants with AAA [25,26]. Antibiotics are frequently not tolerated in long-term use and cyclooxygenase inhibitors have been associated with increased cardiac events [27].

3.3 Preliminary Data

3.3.1 The role of Ang II and AT1 in AAA formation

AngII stimulates AT1 to promote a series of molecular changes leading to AAA formation. In a previous NHMRC funded project we implicated AngII in aneurysm formation [28]. In mice, AngII infusion stimulated aneurysm formation, which particularly affects the suprarenal aorta. This effect of AngII has been replicated by numerous investigators in a variety of different animal models [18,29-31]. The incidence of AAA development induced by AngII is greater in mice with similar risk factors to those associated with human AAA, such as male sex, atherosclerosis and dyslipidaemia (e.g. apolipoprotein E deficiency, $ApoE^{-/-}$)

Furthermore, AAA induced by AngII is:

I. Associated with up-regulation of the aortic expression of the pro-inflammatory cytokines; OPG, OPN and (TGF-β1), and increased macrophage recruitment (Figure 2 & Figure 3) [28]
II. Associated with up-regulation of MMP-9 (Figure 3)
III. Inhibited by ligation of the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ, Figure 4). The mean suprarenal aortic diameters were 2.1±0.1 (n=27) and 1.6±0.1mm (n=27) in $ApoE^{-/-}$ mice infused with AngII and treated with vehicle control or a PPARγ ligand respectively (p=0.01). PPARγ ligation inhibits the ability of AngII to up-regulate OPG, OPN, matrix metallo-protienase-9 (MMP-9) and TGFβ-1 (Figure 4) [28]. Mean TGFβ-1 concentrations in the suprarenal aortas of 27 vehicle control and PPARγ ligand treated AngII-infused $ApoE^{-/-}$ mice were 3.13±3.88 and 0.78±1.06ng/mg protein respectively (p=0.01).

We have previously demonstrated that OPG stimulates an aneurysm phenotype in endothelial cells, vascular smooth muscle cells (VSMCs) and monocytes by promoting inflammation, VSMC

apoptosis and release of MMP-9 [32,33]. Furthermore, both OPN and OPG deficient mice are relatively resistant to the AAA induction by AngII (the mean maximum aortic diameters were 1.5±0.2 (n=29) and 1.3±0.1mm (n=29) in wild type and $OPG^{-/-}$ mice infused with AngII, p=0.01) [30]. OPG and TGFβ-1 themselves stimulate up-regulation of AT1, leading to further downregulation of PPARγ and promotion of macrophage recruitment, matrix degradation and AAA formation (Figure 6, Figure 7 and Figure 8). Together these data provide a pathway by which AngII, TGFβ-1, OPG, OPN and MMP-9 collaborate in stimulating AAA. The pathway can be interrupted using AT1 blockers and PPARγ ligands (Figure 8). AT1 blockade thus completely abolishes the development of AAA in AngII-infused $ApoE^{-/-}$ mice [31]. Thus AT1 is an attractive target for inhibiting the ability of AngII to promote AAA (Figure 1), [18, 29-31].

Studies conducted using cultured human and mice cells, in addition to explants of human AAA biopsies, provide evidence that AngII binds to AT1 to promote downregulation of PPARγ by a TGFβ-1 dependent mechanism (Figure 5). In turn AT1 blockade and PPARγ ligation inhibits OPG and MMP-9 secretion by AAA explants (Figure 6 & Table 1).

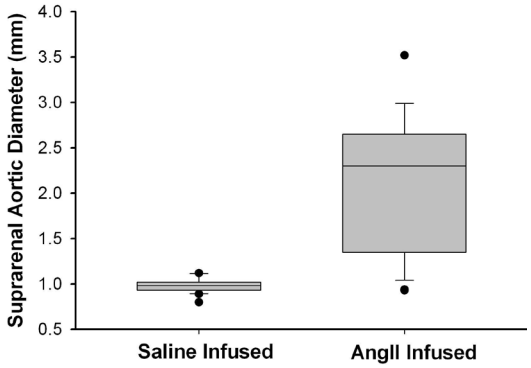

Figure 1 **AngII stimulates aneurysm formation in ApoE-/- mice. Box plots illustrate median and inter-quartile range of maximum suprarenal aortic diameter in 17 week old male saline infused (n=22) and AngII infused (n=27, 1μg/kg/min) ApoE-/- mice**

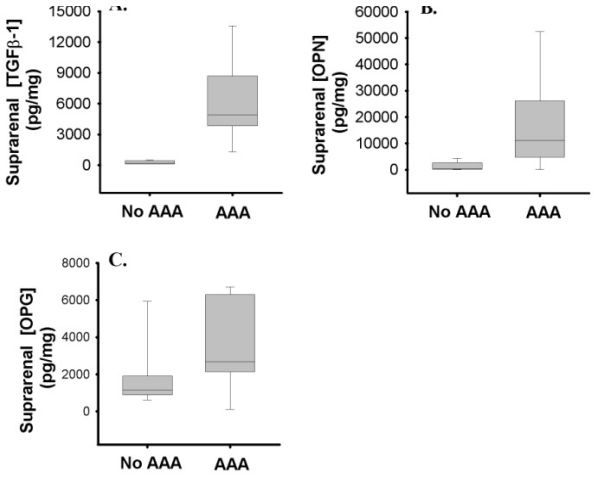

Figure 2 **Comparison of suprarenal aortic concentration of TGFβ-1 (A), OPN (B) and OPG (C) in nine ApoE-/- mice that did and nine ApoE-/- mice that did not develop AAAs following AngII infusion. Cytokine concentrations were measured by ELISA and were significant**

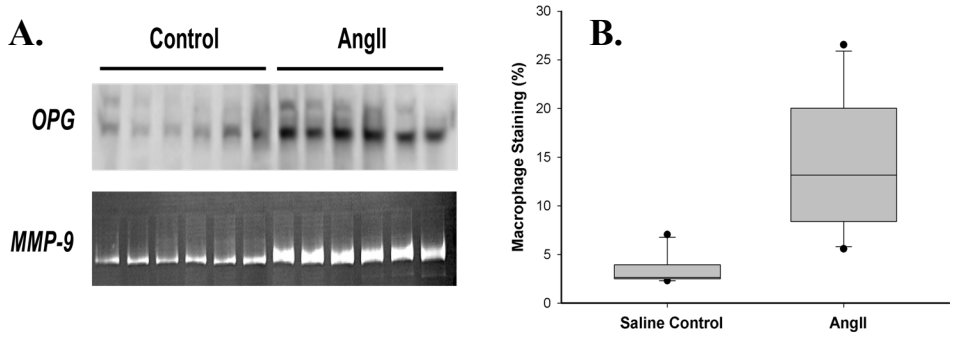

Figure 3 **AngII stimulates up-regulation of OPG (western blotting) and MMP-9 (zymography) (A.), and macrophage recruitment in the aorta of ApoE-/- mice (B.). Macrophage staining was assessed by immunohistochemistry on sections from the suprarenal aortas of ApoE-/-**

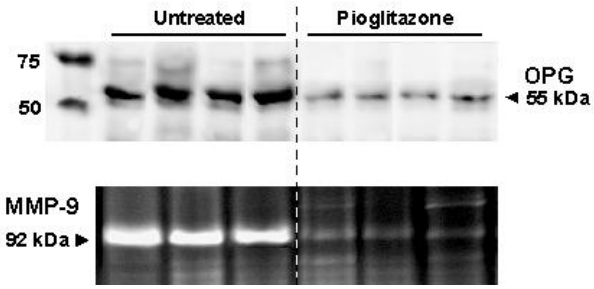

Figure 4 Effect of PPARγ ligation on aortic OPG (western blotting) and MMP-9 (zymography), in an AngII infusion ApoE-/- mouse model of AAA

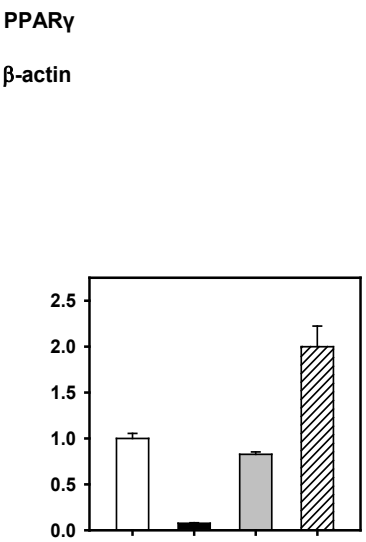

Figure 5 AngII decreases PPARγ protein in cultured aortic VSMCs. VSMCs were incubated with either vehicle, AngII (1μM), AngII+TGFβ-1 blocking antibody or AngII+AT1 blocker for 24h. Total cell lysates were analysed by Western blot (n=5). Results are shown as Mean±SEM

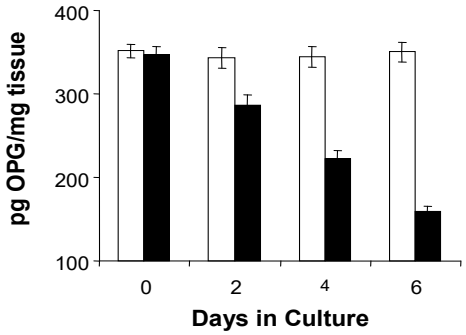

Figure 6 OPG secretion by AAA explants is suppressed by incubation with AT1 blocker (closed bars) compared to control (open bars). Mean±SEM, n=6; p<0.001

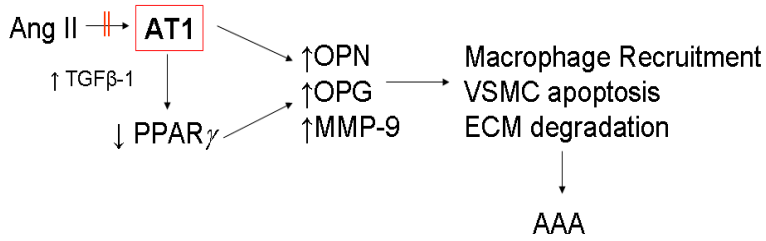

Figure 7 **Interaction of AngII, AT1, TGFβ-1, OPN, OPG and MMP-9 in AAA. The pathway can be opposed by AT1 blockade**

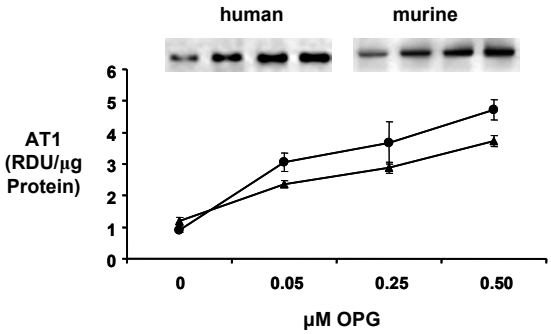

Figure 8 **Dose-dependent induction of AT1 expression in human (●) and murine (▲) aortic VSMCs by OPG over 48 hours. Mean±SEM of triplicate cultures; P<0.01**

Table 1 **PPARγ ligation inhibits OPG and MMP-9 in explants of human AAA**

	n	Secreted OPG*	Explant OPG†	Secreted MMP-9†
Control	8	6.79±0.96	1.02±0.10	1.20±0.04
PPARγ ligation	8	3.08±0.39‡	0.51±0.05‡	0.42±0.01‡

Data are presented as mean±SEM where: *pM per mg tissue; † relative density units (RDU) per µg; ‡ p<0.01 compared to control

3.3.2 AT1 stimulated promotion of TGFβ-1, OPG, OPN and MMP-9 in AAA

A large number of additional findings by our group and others support the importance of the AngII promoted pathological pathway outlined above and in Figure 8.

I. The concentration of a variety of AngII producing enzymes, including angiotensin converting enzyme (ACE) and chymase are increased in biopsies of human AAA, and inhibiting these enzymes antagonises development of AAA in animal models [34-38] and reduces aortic root dilatation in humans [39,40]
II. Elevated concentrations of MMP-9 have been coincidentally linked with human AAA, and deficiency of MMP-9 inhibits AAA development in mice [18,41,42]
III. We have associated AT1 genetic polymorphism with AAA in three geographically disparate populations including 1226 AAA cases and 1723 controls (AGTR1 1166C allele was associated with AAA; adjusted odds ratio 1.60, 95% CI 1.32-1.93, $P=1.1x10^{-6}$) [43]
IV. Serum concentrations of OPG and OPN are elevated in participants with AAA and positively associated with the rate of AAA progression after adjusting for other risk factors [33,44]
V. An interaction between AngII, TGFβ-1, OPG and OPN in promoting cardinal features of AAA, such as inflammation and extracellular matrix destruction, is confirmed in multiple *in vitro* and animal studies [45-48]
VI. Importantly, AT1 blockade has been demonstrated to inhibit AAA development in 3 independent animal models of AAA [31,48,49]
VII. Studies by other investigators also confirm that stimulation of the AT1 promotes inactivation of PPARγ [50]. The importance of PPARγ in protecting the abdominal aorta from aneurysm is supported by further preliminary data from our group and also studies by other investigators. The mean suprarenal aortic diameters were 1.2±0.1 (n=12) and 0.9±0.1 mm (n=12) in low density lipoprotein deficient mice infused with AngII and treated with vehicle control or a PPARγ ligand respectively, p=0.01. Similarly the PPARγ ligand rosiglitazone inhibits AAA formation and rupture in another mouse model [51]

4 Rationale for a medical trial of telmisartan in participants with small AAA

Based on all the preliminary data presented above, a medication which blocks the AT1 would appear to be an ideal therapy to reduce AAA progression. We prefer this approach to one based on ACE inhibition for a number of reasons:

I. ACE inhibition unlike AT1 blockade will only indirectly inhibit the pathway outlined in Figure 8, and since a number of non-ACE AngII producing enzymes have been identified in human AAA biopsies [34,38], it would only be expected to partially inhibit the progression of AAA
II. Much of the blood pressure lowering effect of ACE inhibitors appears to be due to increased circulating kinins [52]. This indirect approach does not fit with current evidence regarding the appropriate target to inhibit AAA progression (Figure 7)
III. To further assess the potential value of AT1 blockade we studied 45 subjects (mean age 70±8 years, 29 male) with small AAAs (mean initial orthogonal diameter 39±10 mm) using CTA and reproducible work-station, semi-automated measurement techniques as previously described [53-56]**.** Participants underwent repeat CTA at a mean of 20±18 months later, and AT1 blocker prescription was associated with reduced AAA expansion as measured by increase in orthogonal aortic diameter (Table 2). This finding combined with the compelling data outlined earlier requires urgent investigation in a randomised controlled trial.

Table 2 Mean infrarenal aortic dimensions and their changes for participants who were and were not prescribed AT1 blockers during follow-up by repeat CTA

AT1 blocker prescribed	Yes (n=11)	No (n=34)	P Value
Orthogonal aortic diameter at baseline (mm)	39±7	40±8	0.71
Follow-up (months)	27±21	24±16	0.51
Annual orthogonal aortic diameter increase (mm/yr)	-0.9±4.2	2.1±2.6	0.01
Annual total infrarenal aortic volume (cm^3/yr)	4.2±3.5	6.2±5.9	0.27

Data presented as Mean±SD increases in aortic dimensions

Telmisartan is a potent long acting AT1 blocker and also acts as a PPARγ ligand [57,83]. New data from our group and others have emphasised the potential value of PPAR gamma activation in limiting AAA progression [51,81]. Telmisartan has PPAR agonist activity that is considerably greater than other AT1 blockers, in addition to its angiotensin receptor blocker actions [83,84]. The agent therefore would be expected to be highly efficacious. A randomised controlled trial of telmisartan in participants with small AAAs is also feasible since ATI blockers are not routinely indicated in these participants currently. AT1 blockers have been in use in participants with arterial disease for over a decade. Many trials have demonstrated telmisartan to be well tolerated [90-92].

5 RESEARCH PLAN

5.1 Study overview

TEDY is an international multi-centre, randomised, double-blind, placebo-controlled clinical trial. Three hundred participants with small AAAs will be randomised to either 40mg of telmisartan or an identical placebo, both given daily for 24 months. The efficacy of telmisartan will be assessed by ultrasound at entry, 6, 12, 18 & 24 months. Treatment(s) other than telmisartan or placebo will be according to accepted international guidelines.

5.2 Inclusion / Exclusion Criteria

The study will include participants who provide written informed consent and have;

1. AAA measuring a maximum diameter of 35-49 mm on CTA or ultrasound.
2. No current indication for AAA repair according to the treating physician or expectation that this will be revised within the next year
3. High likelihood of compliance with treatment over 24 months
4. No contraindications to study treatment, including: renal impairment (i.e. creatinine >1.5x upper limit of normal [ULN]), known significant renal stenosis (>70%) of one or both renal arteries, chronic liver disease (i.e. cirrhosis or hepatitis) or abnormal liver function (i.e. ALT 1.5xULN), electrolyte imbalance and gout
5. No current or planned usage of an AT1 blocker or ACE inhibitors
6. No Previous abdominal aortic surgery.

5.3 Randomisation

Randomisation will be stratified by-site and aortic diameter (35-39, 40-44, 45-49mm) centrally. Since other risk factors have not been consistently shown to predict AAA growth [61], stratification will be limited to initial AAA diameter. Allocation concealment will be achieved by

employing identical packaging and format of active and placebo tablets. Treatment other than telmisartan or placebo will be according to accepted international guidelines.

5.4 Outcome assessment

Outcome assessment will be performed over 24 months. Both outcome assessors and participants will be blinded to treatment allocation. Assessments will include clinical consultation and assessments of drug compliance and side-effects. Participants will be imaged by ultrasound at entry, 6, 12, 18 and 24 months and by CTA at entry, 12 & 24 months. All entry and follow-up information will be recorded on paper case report forms. Blood collected (for experimental purposes) at entry, 6, 12 & 24 months will be sent to the TEDY Coordinating Centre (JCU, Townsville) as will all CTA images. The outcome measures will include:

5.4.1 Primary efficacy endpoint

Change in AAA growth by maximum diameter on ultrasound. Ultrasound measurements will be undertaken at entry, 6, 12, 18 and 24 months.

5.5 Secondary efficacy endpoints

These will be the growth rate of the AAAs assessed by:

I. Changes in maximum orthogonal diameter and maximum infra-renal aortic volume on CTA. CTA will be obtained at entry, 12 and 24 months depending on local ethics guidelines (CTA at entry and 24 months only for Stanford and Leiden study centres).
II. Change in serum OPG, OPN, MMP-9 and TGFβ-1 and D-Dimer on repeated samples over 24 months;
III. Quality of life assessed by the SF36 (Quality of Life) questionnaire completed at entry, 12 & 24 months, which we have previously validated for use in elderly participants [62-64];
IV. There is increasing evidence that the efficacy of medications vary between individuals, with a growing interest in pharmacogenetics [75]. We have previously shown an association between genetic polymorphism in AT1 and AAA [43]. We will assess the presence of the AT1 1166C single nucleotide polymorphism (previously consistently associated with AAA) in recruited participants. This will enable us to analyse the impact of this polymorphism on response to telmisartan.
V. Changes in mRNA expression as previously described [88, 89]. This will allow us to identify precisely how participants are responding to the treatment. This may ultimately identify which participants are more responsive to the medication and should be treated.

As determined in our preliminary cohort, the following will increase the accuracy of outcomes:

I. A core imaging laboratory will be employed in which CTAs will be reconstructed in order to measure aortic volume and maximum aortic diameter in the orthogonal plane. We have developed a semi-automated and highly reproducible system for these assessments, which has previously been described in detail [53-56]**.** Briefly, CTA images are transferred to a work-station and using previously validated thresholding, the aorta (including wall, thrombus and contrast) is defined from the lowest renal artery to the aortic bifurcation. Computer estimated volumes are then automatically generated. Next a line through the axis of the aorta is computer generated and used as a reference to define orthogonal maximum infrarenal aortic diameter. We have previously assessed the reproducibility of aortic volume measurements and found that for intra-observer readings the concordance correlation coefficient (CCC) was 0.99 (n=16, 95% CI 0.99–0.99)

and the mean coefficient of variation (CV) was 2.9% (range 0.1-10.1%). For inter-observer reproducibility the CCC was 0.99 (n=12, 95% CI 0.99–0.99) and the mean CV was 4.3% (range 1.5-10.8%) [55]. We have recently repeated these assessments by two observers on 32 participants and found inter-observer CCC and CV of 0.99 (95% CI 0.97-0.99) and 3.5% for orthogonal diameters and 0.99 (95% CI 0.98-0.99) and 2.7% for aortic volumes, respectively. The reproducibility will continue to be assessed during trial measurements which will be carried out towards the end of the study from dicom images.

II. All centres contributing to the small AAA registry run by Chief Investigator (Jonathan Golledge) have assessed inter-observer reproducibility of aortic ultrasound and reported limits of agreement <±3mm [44,76,77]. New centres will also be validated. Ultrasound and CT findings will not be used interchangeably but will provide independent assessments of effect [78].

5.6 Follow-up

To facilitate data collection a telephone call will be made from the participating site to participant prior to their follow-up and in the event of their non-attendance. Medication will be marked with local phone numbers to contact in the event of drug related problems and participants will be contacted at intervals during the study to encourage medication compliance and assess safety. During follow-up or hospital admissions, forms will be completed to report:

a) AAA repair, by open, endovascular, elective, emergency and reason for intervention;
b) AAA rupture will be documented at site and aided by flagging of notes and by consultation with General Practitioners if participants are lost to follow-up;
c) Death (by cause) will be defined from death certificates;
d) Myocardial infarction, stroke or cardiovascular death documented at the admitting centre;
e) Withdrawal from study medication (by indication) noted from out-participant attendances;
f) Medication compliance at consultations from pill counts will be recorded as number and/or percentage of tablets used;
g) Drug safety (see below);
h) The use of statins and other medication recorded during follow-up.

5.7 Biological determinants of AAA progression and telmisartan response

We will assess the ability of telmisartan to reduce serum concentrations of OPG, OPN, MMP-9, D-Dimer and TGFβ-1 at 12 & 24 months in comparison to entry. We have based this choice of biomarkers on the detailed previous mechanistic studies we have carried out (see Preliminary Data). We have validated reproducible ELISA assays to measure these biomarkers in previous studies [44,79]. We will also assess the impact of telmisartan on mRNA expression and lipidomic profile in participants at entry, 12 and 24 months. Blood samples have been collected for genetic analysis.

5.8 Trial organisation

The trial will be conducted at from major vascular centres in Australia, The Netherlands and the USA at which participants with small AAAs have been identified as part of their current involvement in a small AAA registry co-ordinated by the Chairman of the Australian and New Zealand Society for Vascular Surgery (ANZSVS) Research Group (JG). The study steering committee (SSC) comprises senior investigators from these centres and recognised experts in

AAA management and clinical. This will be the main policy and decision-making committee for the study and will meet by teleconference on a quarterly basis. The study coordinating centre will be located at the Vascular Biology Unit at James Cook University under the direction of Prof Jonathan Golledge. The Project Manager will coordinate activities across all the participating sites, assisting with local ethics submissions and communication with the local sites (data collection, entry and processing). The Core Imaging/ Biomarker Laboratories are located in Townsville and the Veteran's Administration Palo Alto Health Care System, USA will receive dicom images of the CTA of participants at entry, 12 & 24 months to assess the main outcomes of infrarenal aortic volume and maximum diameter utilizing validated protocols [53-56].
Medication concealment and coordination will be led by PCI Pharma Services. Telmisartan and matching placebo will be available from this centre. The web-based randomisation database will be managed by the Monash Clinical Trials Centre, Melbourne Australia, with an independent randomisation centre at Stanford University. Baseline and follow-up data will be collected via report forms. An independent DSMB will review adverse events and conduct an interim analysis. A publications committee will oversee the preparation of reports arising from the study (Figure 9).

5.9 Organisation of individual participant visits and assessments

Participation in this project will involve six (6) visits to the recruitment centre and four (4) phone consultations (Figure 10).

5.9.1 Visit 1, Consent and screening

This appointment is to decide if it is appropriate for the participant to be involved in this research study and to begin data collection. This visit will include the following:

- Informed consent: A Participant Information and Consent Form specifically written for this study will be provided to the potential participant and the study explained in detail. Informed consent will be obtained if the participant wishes to proceed with the study.
- Medical examination: A routine medical examination will be performed and the participant will be asked about the current medications they are taking.
- Quality of life questionnaire: The participant will be asked to answer a short health survey regarding their general health and well−being.
- Ultrasound: An ultrasound will be taken of the participant's AAA.
- Blood test: A sample of blood (24mL) will be collected for measurement of fasting lipids, sugar, inflammation markers, liver and kidney function.
- Blood collection: A sample of blood (24mL) will be collected for experimental purposes. Factors in circulation, mRNA and DNA will be analysed as outlined in this protocol.
- CTA: A CTA scan will be completed of the participant's abdomen in order to allow detailed measurements of the size of the AAA and iliac arteries.
- Physical assessments: Measurement of height, weight, waist and hip circumference, resting brachial blood pressure and heart rate.
- Resting Ankle-brachial Index: This test is done by measuring the blood pressure at the ankle and in the arm, while the participant is lying down.

5.9.2 Visit 2, Enrollment

At the completion of visit 1, consenting and eligible participants will be assigned a randomisation number and randomly allocated to either; the medication telmisartan (40mg daily) or placebo (daily) for 24 months. Participants will then receive their allocated study medication and instructed on the dosing regime.

Numbers of participants not eligible or unwilling to participate will be recorded.

5.9.3 Phone Call, 2 weeks

The participant will be contacted by a member of the study team via phone. The purpose of this call is to assess if they have had any major problems since recruitment. The participant will be questioned about their health in relation to the known medication side-effects (Section 6). This will include any symptoms suggestive of hypotension, such as dizziness. The coordinator will check that the participant is continuing to take the allocated tablet daily.

5.9.4 Visit 3, 3 months

This visit will involve;

- Medical examination: A routine medical examination will be performed and the participant will be asked about the current medications they are taking. The participant will also be asked if they have had any major problems since their last visit. Smoking status will also be checked.

- Recording of Adverse Events and Compliance: The participant will be asked if they have been having trouble with any side effects since the start of the study. The participant will also be questioned regarding the amount and time the study medication is taken to ensure compliance with medication instructions.
- Blood test: A sample of blood (24mL) will be collected for measurement of fasting lipids, sugar, inflammation markers, liver and kidney function.
- Physical assessments: Measurement of weight, waist and hip circumference, blood pressure and heart rate.
- Recording of Event Outcomes: Any significant vascular events experienced since visit 1 will be recorded.

5.9.5 Visit 4, 6 months

This visit will involve;

- Recording of Adverse Events and Compliance: The participant will be asked if they have been having trouble with any side effects since the start of the study. The participant will also be questioned regarding the amount and time the study medication is taken to ensure compliance with medication instructions.
- Ultrasound: An ultrasound will be taken of the participant's AAA.
- Blood collection: A sample of blood (24mL) will be collected for experimental purposes. Factors in circulation and mRNA will be analysed as outlined in this protocol.
- Physical assessments: Measurement of weight, waist and hip circumference, blood pressure and heart rate.
- Recording of Event Outcomes: Any significant vascular events experienced since visit 3 will be recorded.
- Collection and Return of Medication: Participants will be instructed (prior to the visit) to return any unused study medication and all empty bottles. A new prescription for study medication will be issued and participant's directed to the study centre's pharmacy to collect it.

5.9.6 Phone Call – 9 months

The participant will be contacted by a member of the study team via phone. The purpose of this call is to assess if they have had any major problems since recruitment. The participant will be questioned about their health in relation to the known medication side-effects (Section 6). This will include any symptoms suggestive of hypotension, such as dizziness. The coordinator will check that the participant is continuing to take the allocated tablet daily.

5.9.7 Visit 5, 12 months

This visit will involve;

- Medical examination: A routine medical examination will be performed and the participant will be asked about the current medications they are taking. The participant will also be asked if you have had any major problems since their last visit. Smoking status will also be checked.
- Physical assessments: Measurement of weight, waist and hip circumference, resting brachial blood pressure and heart rate.
- Ankle-brachial Index: As described in visit 1.

- Recording of Adverse Events and Compliance: The participant will be asked if they have been having trouble with any side effects since the start of the study. They will also be asked if they are taking the right dose of the medication at the right times.
- Quality of life questionnaire: The participant will be asked to answer a short health survey regarding their general health and well-being.
- Ultrasound: An ultrasound will be taken of the participant's AAA.
- Blood test: A sample of blood (24mL) will be collected for measurement of fasting lipids, sugar, inflammation markers, liver and kidney function.
- Blood collection: A sample of blood (24mL) will be collected for experimental purposes. Factors in circulation and mRNA will be analysed as outlined in this protocol.
- CTA: A CTA scan will be done of the abdomen in order to allow detailed measurements of the size of the participant's AAA.
- Recording of Event Outcomes: Any significant vascular events experienced since visit 4 will be recorded.
- Collection and Return of Medication: Participants will be instructed (prior to the visit) to return any unused study medication and all empty bottles. A new prescription for study medication will be issued and participant's directed to the study centre's pharmacy to collect it.

5.9.8 Phone Call – 15 months

The participant will be contacted by a member of the study team via phone. The purpose of this call is to assess if they have had any major problems since recruitment. The participant will be questioned about their health in relation to the known medication side-effects (Section 6). This will include any symptoms suggestive of hypotension, such as dizziness. The coordinator will check that the participant is continuing to take the allocated tablet daily.

5.9.9 Visit 6, 18 months

This visit will involve;

- Recording of Adverse Events and Compliance: The participant will be asked if they have been having trouble with any side effects since the start of the study. They will also be asked if they are taking the right dose of the medication at the right times.
- Ultrasound: An ultrasound will be taken of the participant's AAA.
- Physical assessments: Measurement of weight, waist and hip circumference, blood pressure and heart rate.
- Blood collection: A sample of blood (24mL) will be collected for experimental purposes. Factors in circulation and mRNA will be analysed as outlined in this protocol.
- Recording of Event Outcomes: Any significant vascular events experienced since visit 1 will be recorded.
- Collection and Return of Medication: Participants will be instructed (prior to the visit) to return any unused study medication and all empty bottles. A new prescription for study medication will be issued and participant's directed to the study centre's pharmacy to collect it.

5.9.10 Phone Call – 21 months

The participant will be contacted by a member of the study team via phone. The purpose of this call is to assess if they have had any major problems since recruitment. The participant will be

questioned about their health in relation to the known medication side-effects (Section 6). This will include any symptoms suggestive of hypotension, such as dizziness. The coordinator will check that the participant is continuing to take the allocated tablet daily.

5.9.11 Visit 7, 24 months

This visit will involve;

- Medical examination: A routine medical examination will be performed and the participant will be asked about the current medications they are taking. The participant will also be asked if you have had any major problems since their last visit. Smoking status will also be checked.
- Physical assessments: Measurement of weight, waist and hip circumference, resting brachial blood pressure and heart rate.
- Ankle-brachial Index: As described in visit 1.
- Recording of Adverse Events and Compliance: The participant will be asked if they have been having trouble with any side effects since the start of the study. They will also be asked if they are taking the right dose of the medication at the right times.
- Quality of life questionnaire: The participant will be asked to answer a short health survey regarding their general health and well-being.
- Ultrasound: An ultrasound will be taken of the participant's AAA.
- Blood test: A sample of blood (24mL) will be collected for measurement of fasting lipids, sugar, inflammation markers, liver and kidney function.
- Blood collection: A sample of blood (24mL) will be collected for experimental purposes. Factors in circulation and DNA will be analyzed as outlined in this protocol.
- CTA: A CTA scan will be done of the abdomen in order to allow detailed measurements of the size of the participant's AAA.
- Recording of Event Outcomes: Any significant vascular events experienced since visit 5 will be recorded.
- Return of Medication: Participants will be instructed (prior to the visit) to return any unused study medication and all empty bottles.

6 SAFETY

6.1 Assessment

Participant safety will be assessed at 2 weeks and then at 3 monthly intervals following randomisation. Adverse events may comprise of [93-96];

- Shortness of breath/wheezing
- Swelling of face/lips/tongue or other parts of the body
- Rash/itching/hives on the skin
- Dizziness
- Faintness
- Fatigue

Possible side effects of the medication include;

- Back pain
- Diarrhoea
- Respiratory tract infection
- Sinus inflammation

This will be monitored through the safety assessments and frequent follow-up phone calls. Serious adverse events are any events that;

- Result in death
- Life threatening
- Require/ prolong hospitalisation
- Persistent/ significant disability/ incapacity

6.1.1 Details of safety assessments

Consultation with a physician (medical examination) during which the participant will be questioned regarding known side effects including symptoms of hypotension, peripheral oedema, renal and liver dysfunction. A physical examination (physical assessments) will include assessment of systolic and diastolic blood pressure, heart rate and peripheral oedema. Laboratory tests will include serum chemistry (Alkaline phosphatase, LDH, AST, ALT, GGTP, CPK, glucose, creatinine, total bilirubin, BUN, uric acid, total protein, albumin, sodium, potassium, chloride, bicarbonate, calcium and phosphorus) and haematology (haemoglobin, haematocrit, differential WBC and platelet counts). Any adverse event will be reported to the coordinating centre and carefully monitored throughout the study. In line with other medication trials, serious adverse events will be defined as death, requirement for in-patient hospital treatment and persistent or significant disability.

6.2 Data and Safety Monitoring Board

The Data and Safety Monitoring Board () (DSMB) will consist of one independent epidemiologist, one independent vascular surgeon and an independent statistician. Due to the size of the trial, the committee only expects to meet once half way through the recruitment and at the final stages of the study. The DMC are responsible for reviewing any adverse events (AEs) or severe adverse events (SAEs) in relation to the medication. In the case of an AE and/or SAE the Chief Principal Investigator will deliver a detailed list of the AEs and SAEs to the DMC. In this particular double blinded study the participant code will be broken and the participant's information will be provided only in this case to the DMC. In the case of a SAE the DMC will arrange to meet. The DMC will in particular concentrate on serious events such as AAA rupture. Expected AAA rupture rates for the current study are approximately 1-2% per year based on published data [19]. Rupture rates >5% per year will be considered a cause for concern. In this instance all other outcome data from the study will be analysed including entry and 6 month ultrasound AAA diameters. AAA growth will be compared between placebo and telmisartan groups using this data. The final decision to stop the study will take into account AAA ruptures, AAA growth data and any other serious complications. Based on their findings the DMC will report their decision of the trial to the steering committee.

6.3 STATISTICAL CONSIDERATIONS

6.3.1 Sample size and power calculations

At present there is insufficient preliminary data demonstrating an accurate effect size of AT1 blockers on AAA growth rate. We therefore estimated our sample size based on a clinically relevant reduction of 30% in annual AAA growth rate. Given local AAA growth rates (mean=1.20mm/y, standard deviation=1.16) applicable to the study population we calculated an effect size d=0.36.52. Accordingly, based on t-test analysis, this study requires 126 participants per group (252 in total, power >80%, $\alpha = 0.05$) to detect the hypothesised reductions in AAA growth rate. Taking into account a drop-out rate of approximately 20% we plan to recruit 300 patients.

6.3.2 Data handling

Data will be managed via a central database. Data will initially be collected on paper Case Report Forms (CRF) and entered into a central electronic database by the study coordinators at each site. All data, including signed informed consent forms and completed surveys, will be stored according to the NHMRC/Universities Australia "Australian code for the Responsible Conduct of Research", 2007 and Queensland State Archives legislation (6.8.3.) [97-98]. The raw data will be retained for 15 years in the Chief Principal Investigator's School at James Cook University in a locked filling cabinet and all data on computer will be de-identified. Copies of this raw data will also be stored on CDs which will be kept in this locked filing cabinet.

6.3.3 Data analysis

6.3.3.1 Hypothesis testing

The primary analysis will be based on intention to treat at randomisation. AAA growth will be calculated as previously described [33,44,76,80]. The efficiency of randomisation will be assessed by comparing the distribution of recognised determinants of AAA progression (principally initial aortic size) in the treatment and control group. If necessary analyses will be adjusted for known determinants of AAA growth, as previously described [33,44,76];

6.3.3.2 Biomarkers

A range of statistical methods will be employed including non-parametric techniques, receiver operator characteristic curves and modelling techniques [33,44,76].

6.3.3.3 Health-related quality of life and other outcomes

These results will be compared between treatment and placebo groups using univariate tests and multiple linear regression, to adjust for any differences in baseline values, such as age [62,63]. A comprehensive statistical analysis plan will be prepared prior to analysis.

7 OUTCOMES AND SIGNIFICANCE

This multicentre study will play an important role in the investigation of a potential new medical treatment for AAA. To date only one negative trial examining the medical treatment of AAA with sufficient power has been published world-wide [20]. TEDY will assess the value of a promising medication with significant preliminary data to suggest it can slow aortic destruction and thus offers the possibility of identifying a new treatment modality for an increasingly common condition. Such a finding would support a large trial to assess the value of telmisartan as a new treatment for AAA. The study will also provide important information on biomarkers which predict responsiveness to telmisartan and biomarkers of AAA progression. There is a need to identify validated markers of AAA progression of biological and clinical relevance. This study allows the opportunity to assess a number of biomarkers, previously associated with AAA, with repeat sampling during follow-up (currently not reported for any putative AAA marker). The study may thus also identify circulating markers which can be used to guide management of small AAA and selection for therapy by drugs or surgical interventions.

Steering Committee (SSC) *–Dr Ronald L. Dalman, Professor J Golledge, Professor Jan Lindeman, Professor P Norman, Professor C Reid, Professor P Walker*

Data and Safety Monitoring Board Professor A Tonkin, Dr Jack Walsh, Professor Theo Stijnen	**Trial Coordinating Centre** VBU James Cook University	**Core Imaging & Biomarker Lab** James Cook University Townsville, Australia; and Veteran's Administration Palo Alto Health Care System, CA, USA.
Drug Coordinating Centres:; and Leiter's Pharmacy and Veteran's Administration Palo Alto Health Care System Pharmacy, CA, USA.	**Trial Randomisation Centres:** Monash Clinical Trials Centre, Melbourne Australia; and Stanford University.	

Participating Hospitals	**State**
Royal Brisbane & Women's Hospital	QLD
The Townsville Hospital	QLD
Fremantle Hospital	WA
The Queen Elizabeth Hospital	SA

Publications Committee: Professor J. Golledge, Professor P. Norman, , Professor P. Walker, Professor Philip Walker Dr Jan Lindeman Dr Ronald Dalman

Figure 9 TEDY organisational structure

	Study Time-points										
Assessment	**0 mths**	**0 mths**	**2 weeks**	**3 mths**	**6 mths**	**9 mths**	**12 mths**	**15 mths**	**18 mths**	**21 mths**	**24 mths**
	Visit 1	**Visit 2**	**Phone Call**	**Visit 3**	**Visit 4**	**Phone Call**	**Visit 5**	**Phone Call**	**Visit 6**	**Phone Call**	**Visit 7**
Consent	x										
Enrolment/Randomisation		x									
Blood Test (safety)	x			x			x				x
CT Angiography*	x						X				x
Resting ABI	x						x				x
Blood collection (Study)	x				x		x		x		x
Ultrasound	x				x		x		x		x
Physical assessments	x±			x	x		x		x		x
QoL questionnaire	x						x				x
Medical Examination	x			x			x				x
Collection of study medication		x			x		x		x		
Return of study medication					x		x		x		x
Event outcomes				x	x		x		x		x
AE & Compliance check		x	x	x	x	x	x	x	x	x	x

Figure 10 Study plan. Physical assessments include; resting BP, resting heart rate, weight, hip and waist measurements, ± indicates an additional assessment of height

*Frequency varies by study site according to local approvals.

8 References

1. Semmens JB, Norman PE, Lawrence-Brown MMD, Bass AJ, Holman CDJ. Population-based record linkage study of the incidence of abdominal aortic aneurysm in Western Australia in 1985-1994. Br J Surg. 1998;85:648-652.
2. Tilson MD 3rd. The polymorphonuclear leukocyte and the abdominal aortic aneurysm: a neglected cell type and a neglected disease. Circulation. 2005;112:154-156.
3. Population Health Division. The health of the people of New South Wales. Available at: http://www.health.nsw.gov.au/public-health/chorep/cvd/cvd_aa.htm. Accessed 14/12/07.
4. Timaran CH, Veith FJ, Rosero EB, Modrall GJ, Arko FR, Clagett PG, Valentine JR, Gewertz BL, McCarthy BL, McCarthy WJ. Endovascular aortic aneurysm repair in patients with the highest risk and in-hospital mortality in the United States. Arch Surg. 2007;142:520-524.
5. Miniño A. National vital statistics reports. National Center for Health Statistics. Viewed at http://www.cdc.gov/nchs/data/statab/lcwk9.pdf on 15/9/07.
6. Australian Bureau of Statistics. Causes of Death. At http://www.ausstats.abs.gov.au
7. Fleming C, Whitlock EP, Beil TL, Lederle FA. Screening for abdominal aortic aneurysm: a best-evidence systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2005;142:203-11.
8. Norman PE, Jamrozik K, Lawrence-Brown MM, Le M, Spencer CA, Tuohy RJ, Parsons RW, Dickinson JA. Impact of screening on mortality from abdominal aortic aneurysm: results of a large, population-based randomised controlled trial. BMJ. 2004;329:1259-1262.
9. The UK Small Aneurysm Trial Participants. Long-term outcomes of immediate repair compared with surveillance of small abdominal aortic aneurysms. N Engl J Med. 2002;346:1445-1453.
10. Lederle FA on behalf of the Aneurysm Detection and Management Veterans Affairs Cooperative Study Group. Immediate repair compared with surveillance of small AAAs. N Engl J Med. 2002;346:1437-43.
11. Cao P. Comparison of surveillance vs Aortic Endografting for Small Aneurysm Repair (CAESAR) trial: study design and progress. Eur J Vasc Endovasc Surg. 2005;30:245-51.
12. Ouriel K. Randomized clinical trials of endovascular repair versus surveillance for treatment of small abdominal aortic aneurysms. J Endovasc Ther. 2009; 16 Suppl 1: I94-105.
13. Cao P on behalf of the CAESAR Trial Collaborators. Initial results of the CAESAR study. European Society of Vascular Surgery Annual Meeting. Oslo, Norway, 2009.
14. EVAR trial participants. EVAR versus open repair in patients with AAA. Lancet. 2005;365:2179-2186.
15. Golledge J, Parr A, Boult M, Maddern G, Fitridge R. The outcome of endovascular repair of small abdominal aortic aneurysms. Ann Surg. 2007;245:326-333.
16. Jones WB, Taylor SM, Kalbaugh CA, Joels CS, Blackhurst DW, Langan EM, Gray BH, Youkey JR. Lost to follow-up: a potential under-appreciated limitation of endovascular aneurysm repair. J Vasc Surg. 2007;46:434-440.
17. Epstein DM, Sculpher MJ, Manca A, Michaels J, Thompson SG, Brown LC, Powell JT, Buxton MJ, Greenhalgh RM. Modelling the long-term cost-effectiveness of endovascular or open repair for abdominal aortic aneurysm. Br J Surg. 2008;95:183-190.
18. Golledge J, Muller J, Daugherty A, Norman PE. Abdominal aortic aneurysm. Pathogenesis and implications for management. Arterioscler Thromb Vasc Biol. 2006;26:2605-2613.
19. Powell JT, Greenhalgh RM, Brown L. Final 12-year results of UKSAT Trial. Br J Surg. 2007;94:702-708.

20. The Propranolol Aneurysm Trial. Propranolol for small AAAs. J Vasc Surg. 2002;35:72-79.
21. Schouten O, van Laanen J, Boersma E, Vidakovic R, Feringa H, Dunkelgrün M, Bax J, Koning J, van Urk H, Poldermans D. Statins are associated with a reduced infrarenal abdominal aortic aneurysm growth. Eur J Vasc Endovasc Surg. 2006;32:21-26.

22. Mosorin M, Juvonen J, Biancari F, Satta J, Surcel HM, Leinonen M, Saikku P, Juvonen T. Use of doxycycline to decrease growth of AAAs. J Vasc Surg. 2001;34:606-610.

23. Walton LJ, Franklin IJ, Bayston T, Brown LC, Greenhalgh RM, Taylor GW, Powell JT. Inhibition of prostaglandin E2 synthesis in AAA. Circulation. 1999;100:48-54.

24. Yoshimura K, Aoki H, Ikeda Y, Fujii K, Akiyama N, Furutani A, Hoshii Y, Tanaka N, Ricci R, Ishihara T, Esato K, Hamano K, Matsuzaki M. Regression of AAA by inhibition of c-Jun N-terminal kinase. Nat Med. 2005;11:1330-1338.

25. Smith, S C, Jr on behalf of Healthcare Professionals From the American Heart Association and the American College of Cardiology. AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease. Circulation. 2001;104:1577-1579.

26. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals. Lancet. 2002;360:7-22.

27. Andersohn F, Suissa S, Garbe E. Use of first- and second-generation cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs and risk of acute myocardial infarction. Circulation. 2006;113:1950-1957.

28. Moran CS, Cullen B, Campbell JH, Golledge J. Interaction between angiotensin II, osteoprotegerin, and peroxisome proliferator-activated receptor-gamma in abdominal aortic aneurysm. J Vasc Res. 2008;46:209-217.
29. Daugherty A, Manning MW, Cassis LA. Angiotensin II promotes atherosclerotic lesions and aneurysms in apolipoprotein E-deficient mice. J Clin Invest. 2000;105:1605-1612.

30. Bruemmer D, Collins AR, Noh G, Wang W, Territo M, Arias-Magallona S, Fishbein MC, Blaschke F, Kintscher U, Graf K, Law RE, Hsueh WA. Angiotensin II-accelerated atherosclerosis and aneurysm formation is attenuated in osteopontin-deficient mice. J Clin Invest. 2003;112:1318-1331.
31. Daugherty A, Manning MW, Cassis LA. Antagonism of AT2 receptors augments angiotensin II-induced abdominal aortic aneurysms and atherosclerosis. Br J Pharmacol. 2001;134:865-870.

32. Mangan SH, Van Campenhout A, Rush C, Golledge J. Osteoprotegerin upregulates endothelial cell adhesion molecule response to tumor necrosis factor-alpha associated with induction of angiopoietin-2. Cardiovasc Res. 2007;79:494-505.
33. Moran C, McCann M, Karan M, Ketheesan N, Golledge J. Association of osteoprotegerin with human abdominal aortic aneurysm. Circulation. 2005;111:3119-3125.
34. Nishimoto M. Increased local AngII formation in AAA. Life Sci. 2002;71:2195-2205.

35. Ihara M, Urata H, Kinoshita A, Suzumiya J, Sasaguri M, Kikuchi M, Ideishi M, Arakawa K. Increased chymase-dependent angiotensin II formation in human atherosclerotic aorta. Hypertension. 1999;33:1399-1405.

36. Liao S, Miralles M, Kelley BJ, Curci JA, Borhani M, Thompson RW. Suppression of experimental abdominal aortic aneurysms in the rat by treatment with angiotensin-converting enzyme inhibitors. J Vasc Surg. 2001;33:1057-1064.

37. Inoue N, Muramatsu M, Jin D, Takai S, Hayashi T, Katayama H, Kitaura Y, Tamai H, Miyazaki M. Effects of chymase inhibitor on angiotensin II-induced abdominal aortic aneurysm development in apolipoprotein E-deficient mice. Atherosclerosis. (In press).

38. Takai S, Furubayashi K, Jin D, Miyazaki M. The significance of chymase in the progression of abdominal aortic aneurysms in dogs. Hypertens Res. 2007;30:349-357.
39. Ahimastos AA, Dart AM, Kingwell BA. Angiotensin II blockade in Marfan's syndrome. N Engl J Med. 2008;359:1732.
40. Ahimastos AA, Aggarwal A, D'Orsa KM, Formosa MF, White AJ, Savarirayan R, Dart AM, Kingwell BA. Effect of perindopril on large artery stiffness and aortic root diameter in patients with Marfan syndrome: a randomized controlled trial. JAMA. 2007;298:1539-1547.
41. Golledge J, Tsao PS, Dalman RL, Norman PE. Circulating markers of abdominal aortic aneurysm presence and progression. Circulation. 2008;118:2382-2392.
42. Pyo R, Lee JK, Shipley JM, Curci JA, Mao D, Ziporin SJ, Ennis TL, Shapiro SD, Senior RM, Thompson RW. Targeted gene disruption of matrix metalloproteinase-9 (gelatinase B) suppresses development of experimental abdominal aortic aneurysms. J Clin Invest. 2000;105:1641-1649.
43. Jones GT, Thompson AR, van Bockxmeer FM, Hafez H, Cooper JA, Golledge J, Humphries SE, Norman PE, van Rij AM. Angiotensin II type 1 receptor 1166C polymorphism is associated with abdominal aortic aneurysm in three independent cohorts. Arterioscler Thromb Vasc Biol. 2008;28:764-770.
44. Golledge J, Muller J, Shephard N, Clancy P, Smallwood L, Moran C, Dear AE, Palmer LJ, Norman PE. Association between osteopontin and human abdominal aortic aneurysm. Arterioscler Thromb Vasc Biol. 2007;27:655-660.
45. Ruiz E. Importance of AngII in VSMC apoptosis. Eur J Pharmacol. 2007;567:231-239.
46. Campos AH, Zhao Y, Pollman MJ, Gibbons GH. DNA microarray profiling to identify angiotensin-responsive genes in vascular smooth muscle cells: potential mediators of vascular disease. Circ Res. 2003;92:111-118.
47. Daugherty A, Rateri D, Cassis LA. Role of the renin-angiotensin system in the development of abdominal aortic aneurysms in animals and humans. Ann N Y Acad Sci. 2006;1085:82-91.
48. Habashi JP, Judge DP, Holm TM, Cohn RD, Loeys BL, Cooper TK, Myers L, Klein EC, Liu G, Calvi C, Podowski M, Neptune ER, Halushka MK, Bedja D, Gabrielson K, Rifkin DB, Carta L, Ramirez F, Huso DL, Dietz HC. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. Science. 2006;312:117-121.
49. Inoue N, Muramatsu M, Jin D, Takai S, Hayashi T, Katayama H, Kitaura Y, Tamai H, Miyazaki M. Involvement of vascular angiotensin II-forming enzymes in the progression of aortic abdominal aneurysms in angiotensin II- infused ApoE-deficient mice. J Atheroscler Thromb. 2009;16:164-71.
50. Min Q, Bai YT, Jia G, Wu J, Xiang JZ. High glucose enhances angiotensin-II-mediated peroxisome proliferation-activated receptor-gamma inactivation in human coronary artery endothelial cells. Exp Mol Pathol. 2009 (In press).
51. Jones A, Deb R, Torsney E, Howe F, Dunkley M, Gnaneswaran Y, Gaze D, Nasr H, Loftus IM, Thompson MM, Cockerill GW. Rosiglitazone reduces the development and rupture of experimental aortic aneurysms. Circulation. 2009;119:3125-3132.
52. Cruden NL, Witherow FN, Webb DJ, Fox KA, Newby DE. Bradykinin contributes to the systemic hemodynamic effects of chronic ACE inhibition in patients with heart failure. Arterioscler Thromb Vasc Biol. 2004;24:1043-1048.
53. Golledge J, Wolanski P, Parr A, Buttner P. Measurement and determinants of infrarenal aortic thrombus volume. Eur Radiol. 2008;18:1987-1994.

54. Golledge J, Jayalath R, Oliver L, Parr A, Schurgers L, Clancy P. Relationship between CT anthropometric measurements, adipokines and abdominal aortic calcification. Atherosclerosis. 2008;197:428-434.
55. Jayalath RW, Jackson P, Golledge J. Quantification of abdominal aortic calcification on CT. Arterioscler Thromb Vasc Biol. 2006;26:429-430.
56. Clancy P, Oliver L, Jayalath R, Buttner P, Golledge J. Assessment of a serum assay for quantification of abdominal aortic calcification. Arterioscler Thromb Vasc Biol. 2006;26:2574-2576.
57. Baumhäkel M, Böhm M. Telmisartan prevents cardiovascular events in a broad group of at-risk patients. Expert Opin Pharmacother. 2009 Dec;10(18):3113-7.
58. Zorad S, Dou JT, Benicky J, Hutanu D, Tybitanclova K, Zhou J, Saavedra JM.Long-term angiotensin II AT1 receptor inhibition produces adipose tissue hypotrophy accompanied by increased expression of adiponectin and PPARgamma. Eur J Pharmacol. 2006;15:112-22.
59. Vauquelin G, Fierens F, Ven Liefde I. Long lasting angiotensin type 1 receptor binding and protection by candesartan: comparison with other biphenyl-tetrazole sartans. J Hypertens Suppl. 2006;24:S23-S30.
60. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olofsson B, Ostergren J, Yusuf S for the CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003;362:759-766.
61. Golledge J, Norman PE. Pathophysiology of abdominal aortic aneurysm relevant to improvements in patients' management. Curr Opin Cardiol. 2009;24:532-8.
62. Paul SL, Sturm JW, Dewey HM, Donnan GA, Macdonell RAL, Thrift AG. Long-term outcome in the North East Melbourne Stroke Incidence Study (NEMESIS): Predictors of quality of life at five years post-stroke. Stroke. 2005;36:2082-2086.
63. Sturm JW, Donnan GA, Dewey HM, Macdonell RAL, Gilligan AK, Srikanth V, Thrift AG. Quality of life after stroke: the North East Melbourne Stroke Incidence Study (NEMESIS). Stroke. 2004;35:2340-2345.
64. Sturm JW, Osborne RH, Dewey HM, Donnan GA, Macdonell RAL, Thrift AG. Brief comprehensive quality of life assessment after stroke: the Assessment of Quality of Life (AQoL) instrument in the North East Melbourne Stroke Incidence Study (NEMESIS). Stroke. 2002;33:2888-2894
65. Tsuji, H., Larson, M.G., Venditti, F.J. Jr., Manders, E.S., Evans, J.C., Feldman, C.L. and Levy, D. Impact of reduced heart rate variability on risk for cardiac events: The Framingham Heart Study. Circulation. 1996;94:2850-2855.
66. Cowan, M.J., Pike, K., Burr, R.L., Cain, K.C. and Narayanan, S.B. Description of time- and frequency- domain based measures of heart rate variability in individuals taking antiarrhythmics, beta blockers, calcium channel blockers, and/or antihypertensive drugs after sudden cardiac arrest. Journal of Electrocardiology. 1994;26:1-13.
67. Campbell, B.C., Sturani, A. and Reid, J.L. Evidence of parasympathetic activity of the angiotensin converting enzyme inhibitor, captopril, in normotensive man. Clinical Science. 1985;68:49-56.
68. Flapan, A.D., Nolan, J., Neilson, J.M.M. and Ewing, D.J. Effect of captopril on cardiac parasympathetic activity in chronic cardiac failure secondary to coronary artery disease. American Journal of Cardiology. 1992;69:532-535.
69. Binkley, P.F., Haas, G.J., Starling, R.C., Nunziata, E., Hatton, P.A., Leier, C.V. and Cody, R.J. Sustained augmentation of parasympathetic tone with angiotensin-converting enzyme

inhibition in patients with congestive heart failure. Journal of the American College of Cardiology. 1993;21:655-661.
70. Claridge M, Hobbs S, Quick C, Day N, Bradbury A, Wilmink T. Nonsteroidal antiinflammatory drugs are associated with increased aortic stiffness. Vasc Health Risk Manag. 2005;1:149-153.
71. Länne T, Sonesson B, Bergqvist D, Bengtsson H, Gustafsson D. Diameter and compliance in the male human abdominal aorta: influence of age and aortic aneurysm. Eur J Vasc Surg. 1992;6:178–184.
72. MacSweeney ST. Mechanical properties of abdominal aortic aneurysm and prediction of risk of rupture. Cardiovasc Surg. 1999;**7**:158–159.
73. Wilson K, Bradbury A, Whyman M, Hoskins P, Lee A, Fowkes G, McCollum P, Ruckley CV. Relationship between abdominal aortic wall compliance and clinical outcome: a preliminary analysis. Eur J Vasc Endovasc Surg. 1998;15:472–477.
74. Hoegh A, Lindholt JS. Basic science review. Vascular distensibility as a predictive tool in the management of small asymptomatic abdominal aortic aneurysms. Vasc Endovascular Surg. 2009 Aug-Sep;43(4):333-8.
75. Baudin B. Angiotensin II receptor polymorphisms in hypertension. Pharmacogenomic considerations. Pharmacogenomics. 2002;1:65-73.
76. Golledge J, Karan M, Moran CS, Muller J, Clancy P, Dear AE, Norman PE. Reduced expansion rate of abdominal aortic aneurysms in patients with diabetes may be related to aberrant monocyte-matrix interactions. Eur Heart J. 2008;29:665-672.
77. Golledge J, Clancy P, Jamrozik K, Norman PE. Obesity, adipokines, and abdominal aortic aneurysm – Health in men study. Circulation. 2007;116:2275-2279.
78. Sprouse LR, Meier GH, Parent FN, DeMasi RJ, Gickmnan MH, Barber GA. Is ultrasound more accurate than axial computed tomography for determination of maximal AAA diameter? Eur J Vasc Endovasc Surg. 2004;28:28-35.
79. Smallwood L, Allcock R, van Bockxmeer F, Warrington N, Palmer LJ, Iacopetta B, Golledge J, Norman PE. Polymorphisms of the matrix metalloproteinase 9 gene and abdominal aortic aneurysm. Brit J Surg. 2008;95:1239-1244.
80. Parr A, Mclaughlin S, Mclaughlin M, Golledge J. Aortic calcification and abdominal aortic aneurysm expansion. Atherosclerosis. 2009;202:350.
81. Golledge J, Cullen B, Rush C, Moran CS, Secomb E, Wood F, Daugherty A Campbell JH, Norman PE. Peroxisome proliferator-activated receptor ligands reduce aortic dilatation in a mouse model of aortic aneurysm. Atherosclerosis. In press.
83. Imayama I, et al. Telmisartan downregulates angiotensin II type 1 receptor through activation of peroxisome proliferator-activated receptor gamma. Cardiovasc Res. 2006;72:184-90.
84. Sharma AM. Telmisartan: the ACE of ARBs? Hypertension. 2006;47:822-3.
85. Golledge J, Leicht AS, Crowther RG, Glanville S, Clancy P, Sangla KS, Spinks WL, Quigley F. Determinants of endothelial function in a cohort of patients with peripheral artery disease. Cardiology. 2008;111(1):51-6.
86. Ono Y, Nakaya Y, Bando S, Soeki T, Ito S, Sata M. Telmisartan decreases plasma levels of asymmetrical dimethyl-L-arginine and improves lipid and glucose metabolism and vascular function. Int Heart J. 2009;50(1):73-83.
87. Rubinshtein R, Kuvin JT, Soffler M, Lennon RJ, Lavi S, Nelson RE, Pumper GM, Lerman LO, Lerman A. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. Eur Heart J. 2010 In press.

88. Wang Y, Barbacioru CC, Shiffman D, Balasubramanian S, Iakoubova O, Tranquilli M, Albornoz G, Blake J, Mehmet NN, Ngadimo D, Poulter K, Chan F, Samaha RR, Elefteriades JA. Gene expression signature in peripheral blood detects thoracic aortic aneurysm. PLoS One. 2007;2(10):e1050.
89. Rush C, Nyara M, Moxon JV, Trollope A, Cullen B, Golledge J. Whole genome expression analysis within the angiotensin II-apolipoprotein E deficient mouse model of abdominal aortic aneurysm. BMC Genomics. 2009 Jul 6;10:298.
90. Williams B, Gosse P, Lowe L, Harper R; PRISMA I Study Group. The prospective, randomized investigation of the safety and efficacy of telmisartan versus ramipril using ambulatory blood pressure monitoring (PRISMA I). J Hypertens. 2006 Jan;24(1):193-200.
91. Weber MA. Telmisartan in high-risk cardiovascular patients. Am J Cardiol. 2010 Jan 4;105(1 Suppl):36A-43A.
92. Schumacher H, Mancia G. The safety profile of telmisartan as monotherapy or combined with hydrochlorothiazide: a retrospective analysis of 50 studies. Blood Press Suppl. 2008 Jun;1:32-40.
93. Weber, M. The telmisartan programme of research to show telmisartan end-organ protection (PROTECTION) Programme. J of Hypertens. 2003; 21 (6):37-46.
94. Diener HC, Sacco R, Yusuf S. Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regiments (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: the prevention regime for effectively avoiding second strokes trial (PROFESS). Cerebrovasc Dis. 2007; 23:268-380.
95. Mann J, Schmieder R, McQueen M, Dyal L, Schumacher H, Pogue J, Wang X, Maggioni A, Budaj A, Chaithiraphan S, Dickstein K, Keltai M, Metsarinne K, Oto A, Parkhomenko A, Piegas L, Svendsen T, Teo K, Yusufre. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet. 2008; 372:547-553.
96. Transcend investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet. 2008;372:1174-1183.
97. National Health and Medical Research Council (NHMRC) Australian Research Council. Australian code for the responsible conduct of research. Australian Government 2007.
98. Office of the Queensland Parliamentary Counsel. Queensland Public Records Act 2002, reprinted 1 July 2010.
99. Hayter CL, Bradshaw SR, Allen RJ, Guduguntla M, Hardman DT. Follow-up costs increase the cost disparity between endovascular and open abdominal aortic aneurysm repair. J Vasc Surg. 2005;42:912-8.
100. Moran CS, McCann M, Karan M, Norman P, Ketheesan N, Golledge J. Association of osteoprotegerin with human abdominal aortic aneurysm progression. Circulation. 2005;111:3119-25.
101. Diehm N, Baumgartner I. D-dimer measurement: a useful prognostic marker in surveillance of patients with abdominal aortic aneurysm? Eur Heart J. 2011;32:258-60.
102. Thompson A, Cooper JA, Fabricius M, Humphries SE, Ashton HA, Hafez H. An analysis of drug modulation of abdominal aortic aneurysm growth through 25 years of surveillance. J Vasc Surg 2010;52:55-61.

103. Parr A, McCann M, Bradshaw B, Shahzad A, Buttner P, Golledge J. Thrombus volume is associated with cardiovascular events and aneurysm growth in patients who have abdominal aortic aneurysms. Journal of Vascular Surgery. (2011) 53 1 28-35
104. Golledge J, Muller R, Clancy P, McCann M, Norman PE. Evaluation of the diagnostic and prognostic value of plasma D-dimer for abdominal aortic aneurysm. European Heart Journal (2011) 32 3 354-364
105. Golledge J, Muller R, Clancy P, McCann M, Norman PE. Evaluation of the diagnostic and prognostic value of plasma D-dimer for abdominal aortic aneurysm. European Heart Journal (2011) 32 3 354-364
106. Golledge J, Tsao P, Dalman R, Norman P. Circulating markers of abdominal aortic aneurysm presence and progression. Circulation. (2008) 118 23 2382-2392
107. Moran CS, Cullen B, Campbell JH, Golledge J. Interaction between angiotensin II, osteoprotegerin and peroxisome proliferator-activated receptor gamma in abdominal aortic aneurysm. Journal of Vascular Research. (2009) 46 3 209-217
108. Golledge J, Cullen B, Rush C, Moran C, Secomb E, Wood F, Daugherty A, Campbell J, Norman P. Peroxisome proliferator-activated receptor ligands reduce aortic dilatation in a mouse model of aortic aneurysm. Atherosclerosis. (2010) 210 1 51-56