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An Investigation into Unusual Access Sites for Arterial Endovascular Interventions

by

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A thesis submitted in partial fulfilment of the Requirements for the degree of

Doctor of Philosophy by Published Work

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# Table of Contents

**List of Figures** ................................................................................................................. 4

**Acknowledgements** ........................................................................................................ 5

**Candidate Declaration** .................................................................................................... 7

**Word Count** ..................................................................................................................... 7

**Table of Publications Submitted for Consideration for the Degree of Doctor of Philosophy by Published Work** ................................................................................................. 8

**Statement of the Candidate’s Contribution to the Published Work** ............................... 8

**Table of Additional Publications Submitted as Supplementary Material** ................. 11

**Summary** .......................................................................................................................... 13

**List of Abbreviations** .................................................................................................... 14

**Background** ...................................................................................................................... 15

  **History of Angiography** ................................................................................................. 15

  **Femoral Artery** ............................................................................................................. 15

    Femoral Artery as a Standard Arterial Access Site ......................................................... 16

  **Carotid Artery** ............................................................................................................... 17

    Carotid Artery as an Unusual Arterial Access Site ....................................................... 17

  **Radial Artery** ................................................................................................................. 19

    Radial Artery as an Unusual Arterial Access Site ....................................................... 19

  **Vena Cava** ..................................................................................................................... 21

    Inferior Vena Cava as an Unusual Arterial Access Site ............................................. 21

  **Arterial Endovascular Interventions and the Endovascular Revolution** .............. 23

    Seldinger Technique ....................................................................................................... 23

    Transcatheter Aortic Valve Implantation ...................................................................... 25

    Endovascular Aortic Repair ........................................................................................ 28

    Endoleaks and Endovascular Aortic Interventions ....................................................... 30

**Methods** ........................................................................................................................... 31

**Literature Search** ............................................................................................................. 31

**Data Extraction, Synthesis and Analysis** ........................................................................ 32

  **Meta-Analysis** ............................................................................................................. 32

**Results** ............................................................................................................................. 33

**Carotid Artery** ................................................................................................................ 33

  Transcarotid Transcatheter Aortic Valve Implantation ..................................................... 33

  Transcarotid Endovascular Aortic Repair ..................................................................... 37

**Radial Artery** .................................................................................................................... 39

  Transradial Aortoiliac and Femoropopliteal Interventions ............................................. 39

**Vena Cava** ....................................................................................................................... 41
Appendices ................................................................. 54

Appendix A: Statements of Contribution Signed by All Co-authors .......... 54

Publication 1: A systematic review of transcatheter aortic valve implantation via carotid artery access ......................................................... 54
Publication 2: Carotid Access for Endovascular Repair of Aortic Pathology: A Systematic Review ............................................................. 56
Publication 3: Transcarotid transcatheter aortic valve implantation: A systematic review .......................................................... 59
Publication 4: Transradial Approach for Aortoiliac and Femoropopliteal Interventions: A Systematic Review and Meta-analysis .................. 62
Publication 5: Transcaval approach for endovascular aortic interventions: A systematic review .......................................................... 67
Publication 6: Carotid Access for Aortic Interventions: Genius or Madness? .......................................................... 69

Appendix B: Publications Included in the Thesis .................................... 71

Publication 1: A systematic review of transcatheter aortic valve implantation via carotid artery access ......................................................... 71
Publication 2: Carotid Access for Endovascular Repair of Aortic Pathology: A Systematic Review ............................................................. 86
Publication 3: Transcarotid Transcatheter Aortic Valve Implantation: A Systematic Review ... 99
Publication 4: Transradial Approach for Aortoiliac and Femoropopliteal Interventions: A Systematic Review and Meta-analysis .................. 108
Publication 5: Transcaval Approach for Endovascular Aortic Interventions: A Systematic Review .......................................................... 117
Publication 6: Carotid Access for Aortic Interventions: Genius or Madness? .......................................................... 125

Appendix C: Additional Related Publications Submitted as Supplementary Material ........................................................................ 130

Transcaval Aortic Access Technique .............................................................. 42
Transcaval Endoleak (Embolisation) Repair ..................................................... 45
Transcaval Transcatheter Aortic Valve Implantation ........................................ 45
Transcaval Thoracic Endovascular Aortic Repair ............................................ 45

Conclusions .................................................................................... 46

Carotid Artery as an Unusual Arterial Access Site ........................................ 46
Radial Artery as an Unusual Arterial Access Site ........................................ 46
Vena Cava as an Unusual Arterial Access Site ........................................... 46

Discussion .................................................................................... 47

The Inter-relationship Between the Material Presented .................................... 47
The Significance of the Published Works as a Contribution to Original Knowledge within the Field ............................................................. 47
Limitations of this Work ........................................................................ 47
Future Work .................................................................................... 48

References .................................................................................... 49

Appendices .................................................................................... 54
Appendix D: Bibliography of Published Work by Candidate .............................................. 138

Book Chapters ................................................................................................................ 138
Papers ............................................................................................................................. 139
Abstracts ......................................................................................................................... 155

Appendix E: Figure Copyright ...................................................................................... 162

Figure 1 .......................................................................................................................... 162
Figure 2 .......................................................................................................................... 167
Figure 3 .......................................................................................................................... 168
Figure 4 .......................................................................................................................... 171
Figure 5 .......................................................................................................................... 174
Figure 6 .......................................................................................................................... 175
Figure 7 .......................................................................................................................... 179
Figure 8 .......................................................................................................................... 180

Appendix F: Manuscript Copyright ............................................................................... 185

Publication 1 .................................................................................................................. 185
Publication 2 .................................................................................................................. 186
Publication 3 .................................................................................................................. 187
Publication 4 .................................................................................................................. 188
Publication 5 .................................................................................................................. 189
Publication 6 .................................................................................................................. 190

List of Figures

Figure 1: Femoral Artery Anatomy and the Arterial Supply to the Lower Limbs .............. 16
Figure 2: Internal Carotid Anatomy and the Arterial Supply to the Brain ...................... 18
Figure 3: Radial Artery Anatomy and the Arterial Supply to the Upper Limb ............... 20
Figure 4: Inferior Vena Cava and its Relation to the Abdominal Aorta ......................... 22
Figure 5: Seldinger Technique ....................................................................................... 24
Figure 6: Transcatheter Aortic Valve Implantation ...................................................... 27
Figure 7: Endovascular Aortic Repair ........................................................................... 29
Figure 8: Classification of Endoleaks ........................................................................... 30
Figure 9: PRISMA Flow Diagram for Publication 1 ....................................................... 33
Figure 10: PRISMA Flow Diagram for Publication 3 .................................................... 35
Figure 11: PRISMA Flow Diagram for Publication 2 ................................................... 37
Figure 12: PRISMA Flow Diagram for Publication 4 ................................................... 39
Figure 13: PRISMA Flow Diagram for Publication 5 ................................................... 41
Figure 14: Transcaval Aortic Access Technique 1/3 .................................................... 42
Figure 15: Transcaval Aortic Access Technique 2/3 .................................................... 43
Figure 16: Transcaval Aortic Access 3/3 ....................................................................... 44
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Dearest Phil,

We didn’t get to spend that much time together and selfishly; I wish we had more time. I wanted to learn so much more from you before you passed away. You left a lasting impression that will stay with me always. Thank you for being the perfect role model surgeon, an academic, a gentleman, a sportsman – a truly learned man in all aspects of life. Thank you for introducing me to John, Doug and Mike who worked tirelessly to help me. Most of all though, thank you for supporting me without even knowing me. You were taken far too soon from this world, gone, but never forgotten. This isn’t the work I started in London back in 2006. This isn’t even the work that I started with you in Brisbane in 2014. But this is the work I ended up finishing and I know that you of all people will really appreciate this sentiment. This thesis embodies hard work, perseverance, dedication to the cause and a dogged determination to finish something. RIP Phil. You’re sorely missed.

To Nick and Mike,
Thank you for both for your unreserved support, particularly when I didn’t realise that’s what it was. You gave me my first opportunities which, by a very meandering path, has unexpectedly led to this career as an academic vascular surgeon. I will never forget and will always be grateful.

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Mum,
You made every sacrifice so I could achieve. Thank you.

To my darling wifey and bubs,
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**Candidate Declaration**

I hereby declare that:

(a) the submitted material as a whole is not substantially the same as published or unpublished material that has been previously submitted, or is currently being submitted, for a degree, diploma, or similar qualification at any university or similar institution

(b) no parts of the work submitted have previously been submitted for any such aforementioned qualification

(c) the work submitted includes work conducted in collaboration with others and written statements on the extent of my individual contribution to the material and the conditions and circumstances under which the work was carried out have been provided. These statements have been signed by all collaborating parties and can be found in Appendix A.

Andrew MTL Choong

**Word Count (Excluding Appendices and References)**

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Statement of the Candidate’s Contribution to the Published Work

   Stonier T, Harrison M, Choong AM.
   Impact factor in year of publication (2016) 6.189
   Andrew Choong was the senior and corresponding author for this publication. He conceived and designed the study, analysed and interpreted the data collected by himself and the co-authors, and supervised the writing of the manuscript. The critical revision, final approval, and overall responsibility for this study were also his.

   Stonier TW, Patel K, Bhrugubanda V, Choong AMTL.
   Impact factor in year of publication (2018) 1.179
   Andrew Choong was the senior and corresponding author for this publication. He conceived and designed the study, analysed and interpreted the data collected by himself and the co-authors, and supervised the writing of the manuscript. The critical revision, final approval, and overall responsibility for this study were also his.
Impact factor in year of publication (2018) 2.289
Andrew Choong was the senior and corresponding author for this publication. He conceived and designed the study, analysed and interpreted the data collected by himself and the co-authors, and supervised the writing of the manuscript. The critical revision, final approval, and overall responsibility for this study were also his.

Impact factor in year of publication (2018) 2.986
Andrew Choong was the joint senior author (alongside Barend Mees) for this publication. Andrew Choong conceived and designed the study, analysed and interpreted the data collected by himself and the co-authors, and supervised the writing of the manuscript. The critical revision, final approval, and overall responsibility for this study were also his.
5 Transcaval Approach for Endovascular Aortic Interventions: A Systematic Review.
Wee IJY, Syn N, Choong AMTL.
PMID: 29804907
Impact factor in year of publication (2018) 2.289
Andrew Choong was the senior and corresponding author for this publication. He conceived and designed the study, analysed and interpreted the data collected by himself and the co-authors, and supervised the writing of the manuscript. The critical revision, final approval, and overall responsibility for this study were also his.

6 Carotid Access for Aortic Interventions: Genius or Madness?
Wee IJY, Syn N, Choong AMTL.
Vascular and Endovascular Review Volume 1, Issue 1, Autumn 2018
https://doi.org/10.15420/ver.2018.6.2
Invited publication
Andrew Choong was the invited, senior and corresponding author for this publication. He conceived and designed the study, analysed and interpreted the data collected by himself and the co-authors, and supervised the writing of the manuscript. The critical revision, final approval, and overall responsibility for this study were also his.
Table of Additional Publications Submitted as Supplementary Material

1 Transradial Access for Lower Extremity Peripheral Arterial Disease: “Required Training and How to Get It”

Andrew MTL Choong, Ian JY Wee, Nicholas L Syn, Stanley EK Loh
Endovascular Today November 2018
https://evtoday.com/articles/2018-nov/training-for-proficiency-in-transradial-access-for-lower-extremity-interventions
Invited publication
Given his research expertise in unusual access sites for arterial endovascular interventions as evidenced by his ‘first description in the literature’ publications, backed up by clinical expertise and an established transradial practice, Andrew Choong was invited to submit a manuscript on how to train his peers in transradial access for lower limb intervention. He was the first and corresponding author for this publication. He conceived and designed the study, analysed and interpreted the data collected by himself and the co-authors, and supervised the writing of the manuscript. The critical revision, final approval, and overall responsibility for this study were also his.

2 Endovascular Aneurysm Repair via Carotid Artery Access: A Viable Alternative?

Andrew Choong, Kirtan Patel, Vamsee Bhrughubanda.
ANZ J. Surg. 2013; 83 (Suppl. 1) 111–114
https://doi.org/10.1111/ans.12163
82nd Royal Australasian College of Surgeons Annual Scientific Congress, Auckland, New Zealand, 6th – 10th May 2013 Conference Abstract
3 Transradial Non-coronary Peripheral Endovascular Interventions: A Systematic Review
Max Meertens, Eugene Ng, **Andrew MTL Choong**.
https://www.jstage.jst.go.jp/article/avd/9/Supplement/9_sup.16-00001/_pdf

4 Trans-radial Access for Iliac Intervention: A Systematic Review
Eugene Ng, **Andrew MTL Choong**.
https://www.jstage.jst.go.jp/article/avd/9/Supplement/9_sup.16-00001/_pdf

5 A Systematic Review of Transcatheter Aortic Valve Implantation Via Carotid Access
Ian Wee, Thomas Stonier, Michael Harrison, **Andrew Choong**.
*Heart, Lung and Circulation 2018 Volume 27, Supplement 3, Pages S595*
https://doi.org/10.1016/j.hlc.2018.04.268
27th Annual Congress of the Association of Thoracic and Cardiovascular Surgeons of Asia, Melbourne, Australia, 16th – 19th November 2017 Conference Abstract
Summary

The endovascular revolution has transformed clinical practice with significant benefits to patients, in particular, as minimally invasive treatment options for those who would have previously been deemed inoperable by conventional ‘open’ surgical techniques.

However, it is impossible to perform arterial endovascular interventions without accessing the arterial system first. Despite close to 100 years of technological and procedural improvement, the femoral artery remains the gold standard arterial access site. In those patients where femoral arterial access is contraindicated, alternative access sites have been described. The majority of these access sites are standard alternatives and are already used in routine clinical practice. However, other arterial access sites are more unusual, and their use is potentially more harmful to patients than standard access.

As a vascular, endovascular and aortic surgeon, I have a varied practice that ranges from traditional open surgery to arterial endovascular interventions, creating alternative vascular access for other specialties who may require it and also repairing the complications arising from vascular access as well.

I remain keen to maximise the benefits of endovascular surgery for all my patients, even if femoral arterial access is contraindicated. This led me to investigate unusual arterial access sites for arterial endovascular interventions. Some of the early descriptions in the literature of unusual access sites for arterial endovascular interventions were not just radical but potentially significantly harmful to patients. A lack of pooled contemporary evidence was sorely lacking, and I embarked on this body of work to fill that evidence gap. My ultimate aim was to educate myself and my colleagues who may also require unusual access sites in their clinical practice, whilst keeping patient safety at the forefront and of paramount importance.
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Expansion</th>
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<tbody>
<tr>
<td>CABG</td>
<td>Coronary artery bypass graft</td>
</tr>
<tr>
<td>CCA</td>
<td>Common carotid artery</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>EVAR</td>
<td>Endovascular aortic repair</td>
</tr>
<tr>
<td>IVC</td>
<td>Inferior vena cava</td>
</tr>
<tr>
<td>M:F</td>
<td>Male:Female ratio</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>PRISMA</td>
<td>Preferred reporting Items for systematic reviews and meta-Analysis</td>
</tr>
<tr>
<td>PRISMA-P</td>
<td>PRISMA for systematic review protocols</td>
</tr>
<tr>
<td>TAVI</td>
<td>Transcatheter aortic valve implantation</td>
</tr>
<tr>
<td>TAVR</td>
<td>Transcatheter aortic valve replacement</td>
</tr>
<tr>
<td>TEVAR</td>
<td>Thoracic endovascular aortic repair</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischaemic attack</td>
</tr>
</tbody>
</table>
Background

History of Angiography

The etymology of angiography is derived from the Greek words ἀνγεῖον angeion, "vessel", and γράφειν graphein, "to write" or "record" which is an almost perfect description of what angiography is. Angiography is the imaging of blood vessels and the organs they supply, by the injection of a radio-opaque contrast medium directly into the blood stream, which can then be imaged with additional x-ray based technologies such as fluoroscopy or computed tomography (CT) or non-x-ray based technologies such as magnetic resonance imaging (MRI).

The first ever contrasted x-ray angiogram was a cerebral angiogram performed by Egas Moniz, a Portuguese physician and neurologist, in 1927 (1). Over the last century, arterial endovascular interventions have usually been performed via the femoral artery and this remains the gold standard arterial access site. However, in as early as 1948, Stig Radner performed the first arterial angiography via the radial artery, realising that there were benefits to unusual or alternative access site for arterial endovascular interventions (2).

Femoral Artery

The arterial tree describes the human arterial system that begins, exiting the heart and supplies all the organs and the rest of the human body. The common femoral artery begins as a continuation of the external iliac artery as it exits from beneath the inguinal ligament supplying both lower limbs. The iliac arteries are the two main terminal branches of the abdominal aorta which is itself the main artery leaving the heart.
Femoral Artery as a Standard Arterial Access Site

The femoral arteries have traditionally been used for arterial access for a number of reasons:

1) Superficial and easy to access
2) Consistent anatomical position and surface landmarks
3) Large calibre

However, there are a number of situations where the femoral artery cannot be used, depending on the arterial endovascular intervention planned. If the path to the target vessel or organ is blocked by disease, or if the femoral artery itself is diseased or blocked, then alternative access has to be sought.

*Figure 1: Femoral Artery Anatomy and the Arterial Supply to the Lower Limbs* (BMJ 2012;345:e5208. Copyright permission for reuse in a thesis on Page 162)
**Carotid Artery**

The left common carotid artery (CCA) arises as a branch of the arch of the aorta, the largest blood vessel of the body that comes directly from the heart. The right CCA however, is a branch of the brachiocephalic artery which is itself a direct aortic arch branch. Both these arteries bifurcate into internal and external branches. The external carotid artery supplies the face whereas the internal carotid artery directly supplies the ipsilateral hemisphere of the brain. Combined with the vertebral arteries which come from the subclavian arteries, they complete the circulation to the brain. The internal carotid arteries supply the anterior circulation whereas the vertebral arteries supply the posterior component with further communicating arteries that complete the arterial system known as the Circle of Willis.

**Carotid Artery as an Unusual Arterial Access Site**

The significance of the carotid arteries is that any interference with the blood flow, directly affects the brain and can potentially cause a stroke resulting in permanent disability or death. Therefore, accessing the carotid artery for the purposes of delivering large bore endovascular devices seems not only counter-intuitive but potentially dangerous to patients.

However, as early as 2000, May et al suggested that the CCA, as an access route to the arterial tree, was not only feasible, but safe for the delivery of large bore endovascular devices, in this case, an endoluminal aortic aneurysm repair \(^3\). Their caveat was that “although it is not recommended for routine use, this approach may be useful in some special situations”.

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17
Figure 2: Internal Carotid Anatomy and the Arterial Supply to the Brain
**Radial Artery**

The radial artery is one of two in the upper limb that supplies the hand (the other, usually dominant being the ulnar artery). It is a distal artery which traces its origin via the brachial, axillary and subclavian to either the brachiocephalic artery on the right or the subclavian on the left, which is itself, a direct branch of the aortic arch.

**Radial Artery as an Unusual Arterial Access Site**

The radial artery has long been used to access the arterial system for sampling arterial blood for gas analysis. The first description of radial artery use for angiography was in 1948 but required an open surgical exposure of the vessel and used large 8 to 10 French (Fr) catheters (2). It would be another 40 years before percutaneous coronary angiography was possible (4) with arterial endovascular intervention in the form of coronary artery stenting following just a few years later (5).

Whilst transradial percutaneous coronary intervention is a relatively standard procedure now, its utility as an access site for lower limb endovascular intervention is considered unusual due to the physical distance from the legs as well as the size limitation of the radial artery as an arterial access conduit.
Figure 3: Radial Artery Anatomy and the Arterial Supply to the Upper Limb

(https://commons.wikimedia.org/wiki/File:2127_Thoracic_Upper_Limb_Arteries.jpg Copyright permission for reuse in a thesis on Page 168)
**Vena Cava**

The vena cava is the largest blood vessel of the venous system of the human body, responsible for returning blood to the heart. Within the abdomen, the inferior vena cava (IVC) lies in close proximity to the abdominal aorta but is wholly distinct in its anatomy and physiological function.

**Inferior Vena Cava as an Unusual Arterial Access Site**

To utilise the vena cava to access the arterial tree would require intentional puncture through a separate blood vessel from a different circulatory system, into another blood vessel, before then closing both intentional puncture sites to prevent internal bleeding.

Despite the somewhat radical suggestion of using the inferior vena cava as an arterial access site, particularly in view of the potential complication of significant internal bleeding, in 2013, Halabi et al, in a porcine series, proposed just this method of alternative arterial access (6). And just a year later, Greenbaum et al published their single-centre series of 19 patients describing the use of caval-aortic access for transcatheter aortic valve replacement (TAVR) (7).
Figure 4: Inferior Vena Cava and its Relation to the Abdominal Aorta

Arterial Endovascular Interventions and the Endovascular Revolution

Seldinger Technique

The Seldinger technique was first described in 1953. It revolutionised the approach to arterial endovascular interventions and was arguably the beginning of the endovascular revolution (8). The principle is that of a direct arterial puncture, the delivery of a guidewire into the artery followed by sequential replacement of sheaths over the wire, thereby confirming safe and accurate intra-arterial placement of ever bigger sheaths into the arterial system.
Figure 5: Seldinger Technique

Panel 1 – Arterial Puncture
Panel 2 – Guidewire Introduction
Panel 3 – Needle Withdrawal
Panel 4 – Catheter Introduction
Panel 5 – Guidewire Removal

(https://derangedphysiology.com/main/cicm-primary-exam/required-reading/cardiovascular-system/Chapter%207.5.6/arterial-cannulation-technique
Copyright Permission for reuse in a thesis on Page 174)
Transcatheter Aortic Valve Implantation

Patients with severe aortic valve disease, either a tightened valve (aortic stenosis) or a floppy valve (aortic regurgitation) were managed with open heart surgery and a valve replacement. The first description of a less invasive, endovascular valve replacement was in 2002 (9), and is referred to as a transcatheter aortic valve implantation (TAVI) or transcatheter aortic valve replacement (TAVR). It was originally used a viable alternative for those patients with multiple comorbidities considered at high risk for open surgery (10) although, as technical procedural ability and the devices have improved, so has the uptake and the range of indications.

TAVI via femoral access is the most widely used access route and is less invasive compared to the transapical alternative that requires a ministernotomy. A totally percutaneous procedure is also regularly performed now (11-13). However, approximately 20% of patients suitable for TAVI are not suitable for femoral access (14). There are a number of relative and absolute contraindications to the use of this access route such as pre-existing peripheral vascular disease (iliofemoral arteriopathy, tortuosity, severe calcification, abdominal aortic aneurysm or previous vascular surgery). Alternative access routes to the aortic valve include transapical, transaortic and subclavian/axillary access.

The transapical approach is currently the second-choice access route in many institutions (15). However, this procedure is much more invasive and more akin to a traditional open surgical aortic valve replacement as there is still a need for not only a left anterior minithoracotomy but also a left ventricular apical puncture. Patients with as severe respiratory disease or left ventricular dysfunction or other significant comorbidities are often not suitable for this approach either. Similarly, a transaortic approach requires a general anaesthetic and an upper ministernotomy (16) and is unsuitable in patients with a ‘porcelain aorta’ or severe respiratory disease.

Subclavian (or transaxillary) access has been demonstrated to be a safe approach but can also be precluded by previous coronary artery bypass grafts (CABG) and also by size of the artery and calcification at the aortic arch (17). Modine et al, in 2010, published the first report on TAVI via a carotid artery (18) thereby further confirming, like May et al did with their endovascular aortic aneurysm
repair (EVAR), that it was technically possible to deliver large bore endovascular devices via the carotid artery (3).
Figure 6: Transcatheter Aortic Valve Implantation

Endovascular Aortic Repair

Aortic aneurysms are dilations of the aorta that are twice (or bigger) than their normal diameter. Whilst they can block, causing problems downstream, or shower particles causing blockages distally, the main risk is that they continue to grow and then burst. Without repair, the survival for a ruptured aortic aneurysm is nearly always fatal \(^{(19)}\).

Traditionally, these aortic aneurysms were repaired by open surgery. Access to the abdomen via a laparotomy, the chest via a thoracotomy, or both via thoracolaparotomy (depending on the size and extent of the aneurysm) was performed. The aorta was clamped above and below, the aneurysm resected, and an interposition graft manually stitched in place to replace the diseased segment. This type of surgery is amongst the most invasive that cardiovascular surgeons perform, and many patients are not physiologically fit for such surgery due to pre-existing conditions.

Parodi et al described the deployment of an endovascular stent graft in an infra-renal abdominal aortic aneurysm in 1991, this, the first endovascular aortic repair (EVAR) \(^{(20)}\). 3 years later, in 1994, as a logical evolutionary step, Dake et al used similar technology for the treatment of isolated descending thoracic aortic aneurysms, now commonly referred to as thoracic endovascular aortic repair (TEVAR) \(^{(21)}\). This use of TEVAR for aortic aneurysms limited to the thoracic segment showed significant early promise and over the last 25 years, significant advances in endovascular technology have since allowed for total endovascular repairs of both the aortic arch and the visceral segment of the aorta in selected patients.
Figure 7: Endovascular Aortic Aneurysm Repair

**Panel A – Deployment of the main body**

**Panel B – Cannulating the contralateral limb of the main body**

**Panel C – Deployment of the contralateral limb stent**

**Panel D – Balloon Moulding**

Endoleaks and Endovascular Aortic Interventions

Naturally, with the new EVAR/TEVAR technology, came new and unexpected complications, the foremost of which was defined as an ‘endoleak’ by White et al in 1996 (22). Despite continued incremental improvements in EVAR/TEVAR devices and endovascular technical expertise, the problem of endoleaks persists to this day. Indeed, one of the major criticisms of EVAR devices in particular vs traditional open aortic aneurysm surgery, is the reintervention rate required, almost invariably, for endoleaks.

![Figure 8: Classification of Endoleaks](image)


Whilst debate continues to rage as to the significant of type II endoleaks in particular, embolisation techniques, normally of the feeding lumbar arteries to the aneurysmal sac, are used in current practice, particularly in the presence of aneurysm sac expansion post EVAR. The use of such techniques may require the use of unusual arterial access for these endovascular arterial interventions.
Methods

The exact methodology for each individual study is detailed in the respective publications which can be found in Appendix B. The generic methodology for the studies has been detailed here.

The systematic reviews and meta-analyses where appropriate, were all conducted in accordance with the either the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (23), the PRISMA for systematic review protocols (PRISMA-P) checklist (24) or the Cochrane Handbook for Systematic Reviews of Interventions (25).

Literature Search

The literature searches were conducted independently by a minimum of two investigators. If a study was in doubt, an appeal was made to a third investigator, usually the senior author. Inclusion and exclusion criteria were defined prior to the literature searches and strictly adhered to.

A combination of electronic databases including Medline (via PubMed), OvidSP, Embase, Google Scholar and Cochrane databases were searched to identify all reports describing the intervention in question. Relevant ‘Medical Subject Headings’ (MeSH) search terms were also used and the combined terms were searched in a repetitive and exhaustive manner.

The ‘related articles’ function was used to broaden the search. Based on the title and abstract, cases were sought in which the intervention was described. References of the articles selected were also searched manually for additional studies. No language restrictions were used. Articles published before a certain date were only excluded if it was prior to the first description in the literature of the intervention being studied. Otherwise, the latest date for this search was always clearly defined and the full search strategies available upon request.

A PRISMA flow diagram and checklist was completed for each completed search strategy.
Data Extraction, Synthesis and Analysis

A pre-designed pro forma was used to capture all possible variables and performed on each of the included studies. Post data extraction, data was pooled and synthesised. Simple summary statistic data was compiled on the demographics of the patient populations study and more specific data on the procedural details.

Meta-Analysis

If possible and appropriate, data that was extracted, pooled and synthesised was then meta-analysed. The Mantel-Haenszel method for random-effects meta-analyses was used to estimate pooled odds ratios or mean differences for dichotomous data. Statistical heterogeneity was assessed using the using $I^2$ statistic. All included studies underwent methodology quality scoring using a 9-point checklist as per the Newcastle Ottawa scale. RevMan (Version 5.3, The Cochrane Collaboration, http://community.cochrane.org/help/tools-and-software/revman-5) was used to perform the meta-analysis.
Results

Carotid Artery

Transcarotid Transcatheter Aortic Valve Implantation

Publication 1: A systematic review of transcatheter aortic valve implantation via carotid artery access (26)

![Figure 9: PRISMA Flow Diagram for Publication 1](image-url)
Patient Details
The mean patient age was 76.9 (27 – 91) years and the Male:Female (M:F) ratio was 44:30. The majority of the procedures were carried for severe aortic stenosis, 5 were performed for aortic regurgitation and 1 for a previously implanted and now failed aortic valve. All patients were deemed unsuitable for open aortic valve surgery and also unsuitable for a transfemoral approach due to severe peripheral vascular disease. A transapical approach was not possible due to severe lung disease or pre-existing coronary artery bypass grafts (CABG). A subclavian approach was deemed unsuitable for similar reasons.

Site of Common Carotid Access
The left CCA was most commonly used in 41/74 cases versus the right that was used in 33. There appeared to be no difference in the side used in terms of outcome.

30-Day Neurological Complication Rate
No incidence of clinical stroke was reported although one study did report a new ischaemic lesion found on diffusion weighted MRI \(^{(27)}\). Two transient ischaemic attacks (TIA) were reported but with no permanent neurological deficit \(^{(18)}\) \(^{(28)}\).

30-Day Mortality Rate
The overall mortality was 4.1% (3/74), which compares favourably to both transfemoral and transapical TAVI mortality rates of 7.5% and 11.3% in a large meta-analysis \(^{(29)}\).
Publication 3: Transcarotid transcatheter aortic valve implantation: A systematic review (30)

The need for the update to our first investigation was due to the publication of a further 4 retrospective studies in the intervening period that required an urgent reappraisal of the literature. We were at this point able to exclude case reports. This updated investigation into TAVI via carotid artery access revealed a total of 364 patients derived from 8 studies as compared to 74 patients from 16 studies.

Figure 10: PRISMA Flow Diagram for Publication 3
Patient Details
The mean patient age for the transcarotid TAVI patients was 80.1 (56 – 90) with similar comorbidities to the transcarotid TAVI patient group in our previous study.

Site of Common Carotid Access
Of the 364 patients who underwent a transcarotid TAVI, 72.8% (265) had their TAVI device delivered via the left CCA whilst the remaining 27.2% (99) were delivered via the right CCA. Again, the carotid artery used appeared to have no impact on outcome.

30-Day Neurological Complication Rate
As compared to our earlier study, the neurological complication rate was higher at 3.8% (14/364). In addition to the previously reported TIAs (18, 28), the majority of the neurological complications arose from one study from Debry et al who reported 6 TIAs and 4 strokes (31). Of note, all of their carotid TAVI procedures were performed under general anaesthetic.

30-Day Mortality Rate
In this updated study, whilst still comparable to transfemoral and transapical TAVI mortality rates as per Li et al’s meta-analysis (29), the mortality rate was higher at 6.5% (24/364) made up of 8 deaths that occurred intra-operatively (2.2%) and a further 16 deaths in the post-operative period.

Meta-analyses
With more data, we were also to meta-analyse subgroup data, albeit a small data set, and compare transcarotid and transapical TAVI approaches with respect to mortality and risk of onset of new dialysis treatment. Both showed no difference between the two groups.
Transcarotid Endovascular Aortic Repair


3.2 Patient Demographics, Comorbidities and Pathologies

This investigation into EVAR / TEVAR via carotid artery access only revealed data for 12 patients, extracted from 11 different case reports. Significantly less data is available for EVAR/TEVAR via carotid access compared to TAVI.

Patient Details

The mean patient age was 64.5 years with a M:F ratio of 3:1. 83% (10/12) patients were deemed unsuitable for traditional open surgery due to their comorbidities. 1 patient refused and we were unable to extract relevant data for the last patient. Pre-existing peripheral vascular disease in the aorto-iliac segment was the predominant reason why conventional femoral arterial access could not be used.
Site of Common Carotid Access
The left CCA was accessed in 58.3% (7/12) of the patients with the remaining 41.7% (5/12) accessing the right CCA. Similar to the TAVI studies, the carotid artery used appeared to have no impact on outcome. The study by Estes et al suggested that the left CCA provided procedural convenience and easy of delivery for the right-handed surgeon (33). This was never mentioned in either of the TAVI studies but seems to be a reasonable explanation for the preferential choice of access, all other factors being equal.

30-Day Neurological Complication Rate
In this small cohort there were no strokes reported and only 1 TIA where the patient reported mild left arm weakness post-operatively, was demonstrated to be microembolisation on MRI and resolved days later (34).

30-Day Mortality Rate
There was 1 death in this reported series giving a mortality rate of 8.3% It occurred days post-operation multi-organ failure secondary to acute pancreatitis (35) This was thought to be the result of organ ischaemia in a patient with a past medical history of necrotising pancreatitis and unrelated to the endovascular aortic repair or carotid access.
Radial Artery

Transradial Aortoiliac and Femoropopliteal Interventions

Publication 4: Transradial Approach for Aortoiliac and Femoropopliteal Interventions: A Systematic Review and Meta-analysis\(^{(36)}\)

Figure 12: PRISMA Flow Diagram for Publication 4

Procedural Success

This was defined as angiographically, with a stenosis of less than 30% post procedure. 17 studies reported such data and the mean success rate was 90.9% (81 – 100).

Complication Rate

Importantly, of the 638 patients, who underwent transradial access for lower limb interventions, complications or major adverse events occurred in only 12 patients (1.9%). These complications including distal embolisation, psoas haematoma, radial artery rupture, minor bleeding, and more significantly a stroke. The rate of post-intervention radial artery occlusion was low at 6.4%. In 405 patients where radial artery patency was assessed and reported, 379 patients had patent radial arteries (93.6%) after their procedure.
Meta-analysis

Of the four studies (four cohort studies, three retrospective and one prospective matched) that compared transradial with transfemoral access, we were able to include 114 patients in the transradial arm and 208 in the transfemoral arm. There was a significantly reduced complication rate with the transradial arm [OR 0.25 CI 95% 0.07 to 0.86; p=0.03] and the heterogeneity was low (I² = 0%).
Vena Cava

Publication 5: Transcaval Approach for Endovascular Aortic Interventions: A Systematic Review\(^{(37)}\)

![Flow Diagram](image-url)

**Figure 13:** PRISMA Flow Diagram for Publication 5
Figure 14: Transcaval Aortic Access Technique 1/3

Directing an electric guidewire through the femoral vein into the inferior vena cava towards a snare in the abdominal aorta

(J Cardiol 2018 Jun;71(6):525-533. Copyright permission for reuse in a thesis on page 189)
Figure 15: Transcaval Aortic Access Technique 2/3

Delivering a microcatheter to exchange for a stiff guidewire

(J Cardiol 2018 Jun;71(6):525-533. Copyright permission for reuse in a thesis on page 189)
The technique of transcaval aortic access described varies between operators and institutions but in general, the following principles apply:

Via a femoral venous percutaneous puncture, a guidewire is delivered to the inferior vena cava (IVC). Figure 14. Transcaval access to the abdominal aorta is achieved by electrifying a guidewire and then advancing it into across the IVC and then into the abdominal aorta. A pre-positioned snare in the abdominal aorta is targeted and the guidewire then captured. Figure 15. Together with the enclosing snare, the wire is then advanced into the thoracic aorta. After a Seldinger exchange to a stiff wire, large bore endovascular devices can then be deployed. The caval-aortic tract is then closed with a closure device normally used for ventricular septal defects or patent ductus arteriosi. Figure 16.
Transcaval Endoleak (Embolisation) Repair
90 patients, from six studies, reported transcaval endoleaks repair \(^{(38-43)}\) The pooled analysis demonstrated 83% were male with a mean age of 79.4 ± 6.6 years. A femoral vein puncture was used in the majority of case although 7.8% of patients underwent a transjugular venous approach \(^{(44)}\).

The technical success rate was 94.4% with no reported cases of 30-day mortality, although there were three cases of thrombophlebitis within 30 days \(^{(41, 44)}\). Mean follow-up was 18.4 ±8.2 months with a reintervention rate of 13.3% due to recurrent and persistent endoleaks \(^{(41-44)}\). These did however, eventually resolve.

Transcaval Transcatheter Aortic Valve Implantation
A total of 119 patients derived from two studies \(^{(7, 45)}\) had TAVI devices delivered transcavally. 38.7% were male with a mean age of 79.5 ± 3.6 years. High EuroSCOREs (mean 10.4±9.3), Society of Thoracic Surgery scores (mean 9.3±5.9), multiple comorbidities, and old age (79.5 years±3.6 years) demonstrated that this patient cohort was high risk and were therefore deemed unsuitable for open surgery. Transfemoral access was pre-existing peripheral vascular disease, iliac tortuosity and previous vascular surgery.

The technical success rate was 97.5% with a 30-day mortality rate of 7.6%. The reintervention rate was 1.7% (2/119). One patient required an emergency retrieval of an embolized valve into the left ventricle whereas another, had an embolisation into the aorta \(^{(7)}\).

Transcaval Thoracic Endovascular Aortic Repair
There were two reported transcaval TEVAR repairs \(^{(46, 47)}\) in male patients with thoracic aortic aneurysms. 30-day mortality rate was 0%. 1 patient suffered a Type 1A endoleak which resolved spontaneously in the following postoperative week \(^{(46)}\). No further intervention was required.
Conclusions

Carotid Artery as an Unusual Arterial Access Site
The carotid artery appears to not only be a viable, but also safe unusual arterial access site for large bore arterial endovascular interventions such as EVAR / TEVAR and TAVI. Its use as an access site is associated with a low neurological complication rate which is particularly surprising given its anatomical role as the dominant blood supply to the brain. Whilst we do not necessarily support the contention of those that advocate its use as a new gold standard alternative to femoral access, we suggest rather, this work does support its use from a technical and patient safety perspective.

Radial Artery as an Unusual Arterial Access Site
The radial artery as an access site for lower limb endovascular interventions not only has a comparable technical success rate compared to the standard femoral access site but is also associated with a markedly lower complication rate. Currently, widespread adoption of radial artery access (outside of percutaneous coronary intervention) is limited by the lack of availability to the specialised longer and smaller calibre equipment needed for such interventions. The interventions possible are therefore similarly limited to the proximal lower limb (predominantly iliac lesions). However, there is potential for radial artery access to revolutionise lower limb angioplasty to become ‘day case’ procedures in view of the lower access complication rate and the ease of monitoring a radial artery puncture site versus that of a femoral artery.

Vena Cava as an Unusual Arterial Access Site
The vena cava puncture, into the adjacent aorta, to allow delivery of a large bore endovascular device, with subsequent closure of both vessels, also appear to be a safe unusual arterial access site. The intraabdominal bleeding rate, the biggest theoretical complication of such an approach, does not appear to be significant with a high and comparable technical procedural success rate. This too offers a viable alternative access site in patients whom femoral access is contraindicated.

This programme of research has shown the value and utility of unusual arterial access sites. We recommend that carotid and radial artery access, and the vena cava all be employed as part of a larger armamentarium of all interventionalists requiring alternative arterial access when treating their patients endovascularly.
**Discussion**

The Inter-relationship Between the Material Presented

This body of work represents an original and thorough investigation into unusual access sites for arterial endovascular interventions. Arterial endovascular interventions as described are extremely varied in purpose and method and arguably, there are an unlimited number of different access sites that could be deemed unusual.

What binds this body of work together, particularly with regards to the use of the carotid artery or vena cava for arterial access, is that these access sites at first glance, appear to be not just radical but potentially harmful to patients, the antithesis of the overriding axiom in clinical medicine of “do no harm”. The studies here have not only demonstrated technical feasibility but also a low complication rate as compared to standard femoral arterial access.

However, as is common in the history of medical innovation, the index patients were wholly unsuitable for conventional endovascular techniques and also not fit for traditional open surgery. As such, necessity become the mother of invention. As endovascular equipment, interventionalists’ procedural skill level and familiarity with such unusual alternative access routes improves, we hope we will also see an increased uptake in such procedures.

The Significance of the Published Works as a Contribution to Original Knowledge within the Field

To the best of our knowledge, these studies were the first descriptions of pooled and synthesised evidence describing these unusual arterial sites for arterial endovascular interventions. They represent a significant contribution of original knowledge to the published literature and contemporaneously plugged the evidence gap that existed prior to their publication.

Limitations of this Work

As it stands, no randomised controlled trials exist on the use of carotid/caval access for EVAR / TEVAR / TAVI or radial access for lower limb intervention. Additionally, the trials that do exist, are from the field of percutaneous coronary intervention and
that data has been extrapolated to apply in a wider context. The literature is limited to case series from innovative centres that have driven the development of the use of unusual arterial access sites. Because of this, this programme of research was necessarily limited to systematic review and meta-analytical methodologies. Whilst valid in this context and still a significant contribution to original knowledge within the field of endovascular arterial intervention, these methods are nevertheless inherently prone to a number of biases no matter how well performed\textsuperscript{(48)}. These biases, particularly positive publication bias, have been acknowledged in each individual study. We accept that leading centres describing what they do may not be universally applicable and as such, we are cautious that such good procedural results with a low complication profile can be reproduced in all centres.

**Future Work**

Ultimately, well designed and conducted randomised controlled trials, are required to better understand the utility of each unusual arterial access site as compared to the gold standard femoral access as well as alternatives. To this end, we are preparing in the first instance to run a prospective randomised controlled trial comparing femoral with radial access for isolated aorto-iliac occlusive lesions. We hope to continue to contribute to original knowledge within this field.
References


Appendices

Appendix A: Statements of Contribution Signed by All Co-authors

Publication 1: A systematic review of transcatheter aortic valve implantation via carotid artery access.

Tom STONIER

Publication 1


Andrew Choong was the senior and corresponding author for this publication. He conceived and designed the study, analysed and interpreted the data collected by himself and the co-authors, and supervised the writing of the manuscript. The critical revision, final approval, and overall responsibility for this study were also his.

I agree that Andrew Choong made the aforementioned contributions to this publication

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Tom STONIER

Publication 2

Carotid Access for Endovascular Repair of Aortic Pathology: A Systematic Review.
Stonier TW, Patel K, Bhrugubanda V, Choong AMTL.
PMID: 29428538

Andrew Choong was the senior and corresponding author for this publication. He conceived and designed the study, analysed and interpreted the data collected by himself and the co-authors, and supervised the writing of the manuscript. The critical revision, final approval, and overall responsibility for this study were also his.

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[Epub ahead of print]
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Vamsee BHRUGUBANDA

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Ian Jun Yan WEE

Publication 3

Transcarotid transcatheter aortic valve implantation: A systematic review.
Wee IJY, Stonier T, Harrison M, Choong AMTL.
Review.
PMID: 29499894

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Max MEERTENS

Transradial Approach for Aortoiliac and Femoropopliteal Interventions: A Systematic Review and Meta-analysis.
Meertens MM, Ng E, Loh SEK, Samuel M, Mees BME, Choong AMTL.
PMID: 30086665

Andrew Choong was the joint senior author (alongside Barend Mees) for this publication. Andrew Choong conceived and designed the study, analysed and interpreted the data collected by himself and the co-authors, and supervised the writing of the manuscript. The critical revision, final approval, and overall responsibility for this study were also his.

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Eugene NG

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| Eugene Ng | | 17/2/2020 |
Publication 4

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| Name                            | Signature       | Date     |
| Stanley Loh Eu Kuang            |                 | 10 Feb 2020 |
Miny SAMUEL

Publication 4

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| B. Meer | [Redacted] | 10 FEB 2020 |
Publication 5: Transcaval approach for endovascular aortic interventions: A systematic review.

Ian Jun Yan WEE

Publication 5

Transcaval approach for endovascular aortic interventions: A systematic review.
Wee IJY, Syn N, Choong AMTL.
PMID: 29804907

Andrew Choong was the senior and corresponding author for this publication. He conceived and designed the study, analysed and interpreted the data collected by himself and the co-authors, and supervised the writing of the manuscript. The critical revision, final approval, and overall responsibility for this study were also his.

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Publication 6: Carotid Access for Aortic Interventions: Genius or Madness?

Ian Jun Yan WEE

Publication 6

Carotid Access for Aortic Interventions: Genius or Madness?
Vascular and Endovascular Review
Wee IJY, Syn N, Choong AMTL.
Invited publication

Andrew Choong was the invited, senior and corresponding author for this publication. He conceived and designed the study, analysed and interpreted the data collected by himself and the co-authors, and supervised the writing of the manuscript. The critical revision, final approval, and overall responsibility for this study were also his.

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Nicholas SYN

Publication 6

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| Name                            | Signature       | Date     |
| Nicholas Syn                    |                 | 10 Feb 2020 |
Appendix B: Publications Included in the Thesis

Publication 1: A systematic review of transcatheter aortic valve implantation via carotid artery access
Publication 2: Carotid Access for Endovascular Repair of Aortic Pathology: A Systematic Review
Publication 3: Transcarotid Transcatheter Aortic Valve Implantation: A Systematic Review

* This study was presented as a poster during the Australian and New Zealand Society for Vascular Surgery 2017 conference, and the Asia Society of Vascular Surgeons 2017 conference.

* Corresponding author: Department of Cardiac, Thoracic and Vascular Surgery, National University Heart Centre, 5 Lower Kent Ridge Rd. Singapore 119074, Singapore. E-mail address: suranci@nus.edu.sg (Andrew M.T.L. Choong).

https://doi.org/10.1016/j.jccc.2018.01.090
0914-5037 © 2018 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.
Publication 4: Transradial Approach for Aortoiliac and Femoropopliteal Interventions: A Systematic Review and Meta-analysis
Publication 5: Transcaval Approach for Endovascular Aortic Interventions: A Systematic Review
Publication 6: Carotid Access for Aortic Interventions: Genius or Madness?
Appendix C: Additional Related Publications Submitted as Supplementary Material
Transradial Access for Lower Extremity Peripheral Arterial Disease: “Required Training and How to Get It”
Endovascular Aneurysm Repair via Carotid Artery Access: A Viable Alternative?

82nd Royal Australasian College of Surgeons Annual Scientific Congress, Auckland, New Zealand, 6th – 10th May 2013 Conference Abstract
A Systematic Review of Transcatheter Aortic Valve Implantation Via Carotid Access

27th Annual Congress of the Association of Thoracic and Cardiovascular Surgeons of Asia, Melbourne, Australia, 16th – 19th November 2017 Conference Abstract
Appendix D: Bibliography of Published Work by Candidate

Total (125)

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Kind regards,

Andrew Choong
--
Assistant Professor
National University of Singapore
Consultant Vascular and Endovascular Surgeon
National University Heart Centre, Singapore
-------------
From: Dave Fornell 
Dave.Fornell@wainscotmedia.com

Subject: Re: Image Reproduction in PhD Thesis

Date: 5 May 2020 at 22:11

To: Andrew Mark Choong Tze Liang <suramctl@nus.edu.sg>, Melinda Taschetta-Millane
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...
Kind regards,

Andrew.

--

Asst Prof Andrew MTL Choong
MB BS, FRCS (Gen Surg), FEBVS (Hons), MFSTEd, FAMS (General Surgery)

Assistant Professor
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National University of Singapore

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www.edwards.com
fax: +65 6883 6792
mobile: +65 8399 2458

From: Andrew Mark Choong Tze Liang <suramctl@nus.edu.sg>
Sent: Wednesday, May 6, 2020 2:01 PM
To: Le Tien Doan <LeTien_Doan@edwards.com>

Do I need any other formal approval from you?

Kind regards,

Andrew.

--

Assistant Professor
National University of Singapore

Consultant Vascular and Endovascular Surgeon
National University Heart Centre, Singapore

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Edwards Lifesciences (Asia) Pte Ltd
35 Changi North Crescent
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fax: +65 6883 6792
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From: Andrew Mark Choong Tze Liang <suramctl@nus.edu.sg>
Sent: Wednesday, May 6, 2020 9:00 AM
To: Le Tien Doan <LeTien_Doan@edwards.com>
Subject: [EXTERNAL] Image Reproduction in PhD Thesis

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