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Die Anwendung der Computertomographie zur Größenbestimmung der Klappenprothese vor perkutanem Aortenklappenersatz bei Patienten mit schwerer Aortenklappenstenose

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Abkürzungsverzeichnis

TAVI – trans-catheter aortic valve implantation

TAVR – trans-catheter aortic valve replacement

CT – Computertomographie

EKG – Elektrokardiogramm

ROC – Receiver Operating Characteristic

1. Einleitung

1.1 Hintergrund

Die Aortenstenose ist vor der Mitralinsuffizienz die häufigste Erkrankung der Herzklappen [1]. Während das rheumatische Fieber in Industrieländern anders als in Ländern der dritten Welt als Ursache von Erkrankungen der Herzklappen selten geworden ist [2] und kongenitale Stenosen des aortalen Ausflusstrakts in der Regel bereits im Kindesalter entdeckt werden, ist die Aortenstenose bei Erwachsenen zumeist die Folge eines langandauernden Prozesses mit zunehmender Kalzifikation der Aortenklappe. Es handelt sich daher um eine Erkrankung vorwiegend des älteren Menschen, wobei die Prävalenz kontinuierlich mit dem Alter von unter 1% bei 50-59-Jährigen auf fast 10 % bei Individuen in der neunten Lebensdekade ansteigt [3]. Angesichts der steigenden Lebenserwartung ist zukünftig von einer zunehmenden absoluten Anzahl betroffener Personen auszugehen. Eine von der Normanatomie der trikuspiden Klappe abweichende bikuspide Aortenklappe, welche bei ca. 1-2% aller Neugeborenen auftritt [4], stellt hierfür aufgrund der veränderten Hämodynamik einen besonderen Risikofaktor dar, infolgedessen der Krankheitsprozess um rund zwei Jahrzehnte früher einsetzt [5]. Während die Aortenstenose früher als degenerative Erkrankung infolge eines Alterungsprozesses aufgrund der mechanischen Beanspruchung erklärt wurde, geht man inzwischen von einer Genese ähnlich der Atherosklerose mit chronischer Inflammation, Lipidakkumulation und Kalkeinlagerungen aus, wobei sich die Risikofaktoren beider Krankheitsbilder überschneiden [6]. Auch eine genetische Prädisposition mancher Individuen wird diskutiert [7]. Pathophysiologisch führt die zunächst subklinische, im frühen Stadium als Aortensklerose bezeichnete progrediente Kalzifikation der Klappentaschen schließlich zu einer Verringerung der Klappenöffnungsfläche mit Entwicklung eines Druckgradienten und infolgedessen zu einer Hypertrophie des linksventrikulären Myokards, was

die typische Symptomtrias aus Angina pectoris, Synkope und Herzinsuffizienz erklärt [8]. Während asymptomatische Patienten selbst bei schwerer Aortenstenose eine gute Prognose haben, markiert die Entwicklung von Symptomen einen Wendepunkt im Krankheitsverlauf: Die jährliche Mortalitätsrate dieser Patienten beträgt annähernd 25 % [5].

1.2 Behandlungsoptionen der Aortenstenose

Es gibt derzeit keine effektiven pharmakologischen Behandlungsansätze, die in der Lage sind, den fortschreitenden Krankheitsprozess der Aortenstenose aufzuhalten oder einen notwendigen Klappenersatz hinauszuzögern [9]. So konnte für cholesterinsenkende Therapien, namentlich für die Gabe von Statinen, deren Wirksamkeit bei der Behandlung der koronaren Herzkrankheit gut dokumentiert ist, im Rahmen der Aortenstenose kein klinischer Nutzen nachgewiesen werden, obwohl sich die Ätiologie beider Erkrankungen ähnelt [10-12].

Als palliative Behandlungsoption oder zur Überbrückung bis zur definitiven Therapie kann bei komorbiden Patienten, deren Risikoprofil einen primären Klappenersatz nicht zulässt, eine kathetergestützte Ballonvalvuloplastie durchgeführt werden. Der positive Effekt dieser Maßnahme ist jedoch nur vorübergehend und hält etwa sechs Monate an, ohne dass sich das Langzeitüberleben der Patienten verbessert [13].

Die einzige kurative Behandlung der Aortenstenose ist daher der Ersatz der Aortenklappe, wobei das chirurgische Vorgehen mit Sternotomie, Exzision der Klappe und Einbringen entweder einer mechanischen oder biologischen Klappenprothese in Kardioplegie unter Einsatz der Herz-Lungen-Maschine für lange Zeit die einzige Option darstellte. Mit einer 30-Tages-Mortalität von insgesamt 2-3% bzw. 6% bei über 80-jährigen Patienten, die zudem im Laufe der Zeit deutlich verringert werden konnte, ist der Eingriff als Goldstandard in der Behandlung der Aortenstenose etabliert und

bei adäquater Patientenselektion mit einem beherrschbaren Risiko behaftet. Allerdings sind komorbide Patienten mit multiplen Begleiterkrankungen einem operativen Klappenersatz häufig entweder gar nicht oder nur unter hohem perioperativem Mortalitätsrisiko zugänglich [14]. Zudem wurde mehrfach darüber berichtet, dass bei Patienten mit schwerer Aortenstenose trotz leitliniengerechter Indikation kein operativer Klappenersatz durchgeführt wurde, weil das perioperative Risiko unter anderem wegen des fortgeschrittenen Patientenalters fälschlicherweise als zu hoch eingeschätzt wurde [15, 16].

Als zunächst nur für nicht-operable Patienten entwickelte Alternative wurde erstmals 2002 der perkutane Klappenersatz (trans-catheter aortic valve implantation – TAVI bzw. trans-catheter aortic valve replacement – TAVR) vorgestellt [17], bei dem eine auf einem Stent aufgenähte biologische Klappe mittels eines Kathetersystems in den Aortenannulus eingebracht und unter Verdrängung der erkrankten Klappe entfaltet wird. Dies geschieht in der Regel über einen transfemoralen Zugangsweg, als Alternative ist jedoch auch ein Zugang über die A. carotis, die arteriellen Gefäße der oberen Extremität, transapikal oder direkt über die Aorta thoracalis möglich, wobei die beiden letztgenannten Routen eine Thorakotomie erfordern. Seit ihrer Einführung wurde die Anzahl der verfügbaren TAVR-Systeme ebenso wie die der angebotenen Klappengrößen gesteigert, die Anwendbarkeit vereinfacht und die Komplikationsrate verringert, was insbesondere die Häufigkeit einer postinterventionellen paravalvulären Klappeninsuffizienz betrifft [14]. In mehreren internationalen randomisierten kontrollierten Studien konnte gezeigt werden, dass der perkutane Aortenklappenersatz sowohl ein verbessertes Langzeitüberleben bei nicht-operablen Patienten im Vergleich zur Standardtherapie ermöglicht [18-20] als auch vergleichbare oder sogar bessere Ergebnisse bei nur unter erhöhtem Risiko operablen Patienten erzielt [21-23]. Zudem weisen perkutan ebenso wie chirurgisch eingebrachte Aortenklappen eine im Verlauf von fünf Jahren echokardiographisch unverändert gute Funktion und stabile hämodynamische Parameter auf

[24]. Folgerichtig gilt der perkutane Aortenklappenersatz inzwischen als Therapie der Wahl bei solchen Patienten, die inoperabel oder nur unter hohem Risiko operabel sind, sofern sie für den Eingriff geeignet sind und keine Komorbiditäten vorliegen, die den zu erwartenden Nutzen des Eingriffs überwiegen [25, 26]. Weitere Studien unter Einschluss von Patienten mit behandlungswürdiger Aortenstenose und geringerem Operationsrisiko haben ergeben, dass der perkutane dem operativen Klappenersatz auch in diesem Patientenkollektiv nicht unterlegen ist, wobei hier bislang keine Langzeitergebnisse vorliegen [27-31]. Gemäß den geltenden Indikationen kommen laut Hochrechnungen rund 290000 Individuen in Europa und den USA als Kandidaten für einen perkutanen Aortenklappenersatz in Betracht, wobei jährlich nahezu 27000 mögliche Patienten hinzukommen [32]. Sollten die Indikationen für den interventionellen Klappenersatz zukünftig auf Patienten mit geringerem perioperativem Risiko ausgeweitet werden, würde infolgedessen auch die Anzahl der TAVR-Kandidaten zunehmen.

1.3 Bildgebung vor perkutanem Aortenklappenersatz

Im Gegensatz zum chirurgischen Klappenersatz, bei dem der Aortenannulus der direkten Messung durch den Operateur zugänglich ist, basiert die Auswahl der geeigneten Klappengröße beim perkutanen Klappenersatz auf zuvor mittels bildgebenden Verfahren erfolgten Messungen. Da kathetergestützt eingebrachte Klappenprothesen nicht fest durch Nähte mit der Gefäßwand verbunden sind, sollte ein perkutaner Aortenklappenersatz einen geringfügig größeren Diameter als der Aortenannulus aufweisen, damit eine ausreichende Verankerung der Prothese gewährleistet ist. Die Wahl einer nicht geeigneten Klappengröße kann zu schweren Komplikationen führen: So kann das Einbringen einer zu großen Prothese („Oversizing“) eine nicht ausreichende Entfaltung der Klappe, Störungen des Erregungsleitungssystems mit Notwendigkeit einer

Schrittmacherimplantation oder eine Ruptur des Aortenannulus nach sich ziehen. Auf der anderen Seite kann eine zu kleine Prothese („Undersizing“) embolisieren oder eine paravalvuläre Klappeninsuffizienz begünstigen [33], wobei sich die letztgenannte Komplikation als unabhängiger Risikofaktor für eine erhöhte Mortalität nach TAVR erwiesen hat [34, 35].

Die Anatomie der Aortenwurzel ist komplex und weist mehrere voneinander differenzierbare ringförmige Strukturen auf [36], wobei der eigentliche Aortenannulus als die Ebene zu verstehen ist, welche die Anheftungspunkte der Taschenklappen schneidet und die engste Stelle der Aortenwurzel darstellt [33]. Da der Aortenannulus eine ovaläre Form aufweist, wird seine Größe durch zweidimensionale Messungen, wie sie die transthorakale oder transösophageale Echokardiographie typischerweise liefert, im Vergleich zur dreidimensionalen Darstellung durch die 3D-Echokardiographie oder die kontrastangehobene Computertomographie systematisch unterschätzt [37, 38]. Als Konsequenz kann eine nur auf echokardiographischen Messungen basierende Prothesenauswahl zur Verwendung einer zu kleinen Klappengröße führen, was das häufigere Auftreten einer paravalvulären Insuffizienz nach sich zieht [39-42]. Neben diesem Vorteil gegenüber der 2D-Echokardiographie ermöglicht die Computertomographie nach intravenöser Kontrastmittelgabe eine schnelle und vollständige Evaluation des vaskulären Zugangswegs und der Abgänge der Koronararterien und kann zudem durch Bestimmung eines geeigneten Angulationswinkels für die fluoroskopische Darstellung der Aortenwurzel die Eingriffsplanung vor perkutanem Aortenklappenersatz erleichtern [43].

1.3.1 Bestimmung der optimalen Prothesengröße vor perkutanem Aortenklappenersatz mittels der Computertomographie

Im Gegensatz zur ovalären Form des Aortenannulus weist das die Taschenklappen tragende Gerüst einer perkutan eingebrachten Aortenklappenprothese eine kreisförmige Struktur auf, deren Diameter durch den Hersteller festgelegt ist. Um beide Größen in Beziehung zueinander setzen zu können, ist daher eine Umwandlung der gemessenen Dimensionen des Aortenannulus in einen virtuellen Diameter notwendig, welcher dem Durchmesser eines Kreises gleicher Größe entspricht. Dies kann auf verschiedenen Wegen geschehen: Durch die Berechnung des Mittelwertes des längsten und kürzesten Durchmessers [44], die Bestimmung des Umfangs [45] oder der Fläche des Aortenannulus [46, 47], wobei aus den beiden letztgenannten Messwerten durch eine einfache rechnerische Umformung jeweils der Diameter eines Kreises gleichen Umfanges bzw. gleicher Fläche ermittelt werden kann. Aus der so ermittelten Größe des Aortenannulus lassen sich Empfehlungen für eine geeignete Prothesengröße ableiten. So konnte beispielsweise in einer Studie von *Binder et al.* gezeigt werden, dass ein auf computertomographischen statt nur auf echokardiographischen Messungen basierender Algorithmus zur Auswahl der Prothesengröße bei perkutanem Aortenklappenersatz zu einem selteneren Auftreten einer paravalvulären Insuffizienz führt, wenn dabei ein moderates Oversizing angestrebt wird [40]. Dennoch bleibt die Frage, in welchen Grenzen eine Klappenprothese gegebener Größe für einen bestimmten Patienten geeignet ist, und wann stattdessen eine größere oder kleinere Prothese verwendet werden sollte, um ein optimales Ergebnis zu erzielen. Hinzu kommt, dass neben der Größe des Aortenannulus weitere Faktoren wie etwa das Ausmaß der Verkalkung der Klappentaschen und der Abstand zu den Koronarabgängen bei der Prothesenauswahl von Bedeutung sind. Daher ist die Entscheidung für eine bestimmte Klappengröße das Resultat eines auf allen vorhandenen Informationen basierenden Prozesses, wobei die Auswahl unmittelbar vor der Implantation im Katheterlabor mittels eines zur

Größenbestimmung geeigneten Ballonkatheters bestätigt oder gegebenenfalls korrigiert werden kann [48-50].

1.3.2 Manuelle und assistierte Vermessung des Aortenannulus in der Computertomographie

Die sorgfältige Vermessung der Aortenannulus ist entscheidend für die Auswahl der am besten geeigneten Klappenprothese. Aufgrund des komplexen Aufbaus der Aortenwurzel können die durch die manuelle Evaluation erzielten Resultate auf verschiedene Weise durch eine nicht korrekt angewendete Messmethode verfälscht werden [33]. Folgerichtig unterliegen derartig gewonnene Messergebnisse einer relativ hohen Inter- und Intra-Untersuchervariabilität, darüber hinaus ist der Untersuchungsprozess zeitaufwendig [51, 52]. Softwarelösungen mit halb- oder vollautomatischer Segmentierung der Aortenwurzel bieten daher das Potential, die Vermessung des Aortenannulus sowohl für erfahrene als auch unerfahrene Untersucher zu vereinfachen und besser zu standardisieren, ohne dass relevante Abweichungen zur manuellen Messung durch erfahrene Untersucher auftreten [51-55]. Zugleich lässt sich die Dauer des Auswertungsprozesses deutlich verkürzen [56]. In diesem Zusammenhang ist von Interesse, ob eine erfolgreiche automatische bzw. semiautomatische Segmentierung abhängig von der Bildqualität und dem Grad der Aortenklappenverkalkung ist und inwiefern sich Unterschiede in der Größenmessung zwischen manueller und assistierter Evaluation der Aortenwurzel auf die Wahl der Klappenprothese auswirken.

1.4 Zielsetzung

Im Rahmen der vorliegenden Promotionsarbeit wurden an der Klinik und Poliklinik für Radiologie der Ludwig-Maximilians-Universität München, Standort Großhadern, zwei wissenschaftliche Publikationen verfasst.

In der ersten Arbeit wurde retrospektiv untersucht, inwiefern die Größenbestimmung des Aortenannulus in der Computertomographie bei Patienten mit Aortenstenose vor geplantem perkutanem Aortenklappenersatz dazu geeignet ist, die Größe der letztlich gewählten Klappenprothese vorherzusagen. Aus den so erhobenen Daten wurden zudem Schwellenwerte für verschiedene Prothesengrößen berechnet. Die Ergebnisse wurden in *PLOS ONE* veröffentlicht (Impact Factor 2014: 3,234).

Im zweiten Projekt wurde retrospektiv untersucht, ob die softwaregestützte halbautomatische Vermessung des Aortenannulus in CT-Datensätzen von Patienten mit Aortenstenose vor perkutanem Aortenklappenersatz gleichwertige Ergebnisse verglichen zur manuellen Vermessung durch erfahrene Untersucher liefert bzw. inwiefern diese Ergebnisse miteinander austauschbar sind. Die Studie wurde im *International Journal of Cardiovascular Imaging* publiziert (Impact Factor 2017: 2,036).

Die Dissertationsschrift beschreibt somit zwei verschiedene Aspekte der Anwendung der Computertomographie hinsichtlich der Größenbestimmung der Klappenprothese vor perkutanem Aortenklappenersatz bei Patienten mit Aortenstenose. Die Hypothesen dieser Arbeit waren, dass die Computertomographie zur Bestimmung der am besten geeigneten Klappengröße herangezogen werden kann und dass die halbautomatische Vermessung des Aortenannulus gleichwertige Ergebnisse wie die manuelle Vermessung durch erfahrene Untersucher liefert.

1.4.1 CT-basierte Vermessung des Aortenannulus zur Größenbestimmung der Prothese vor perkutanem Aortenklappenersatz

Für das erste der beiden wissenschaftlichen Projekte wurden retrospektiv die CT-Datensätze konsekutiver Patienten ausgewertet, die zwischen November 2007 und Juni 2012 in der Medizinischen Klinik I (Kardiologie) des Klinikums der Universität München mit einem perkutanen Aortenklappenersatz versorgt wurden. Von den insgesamt 441 in diesem Zeitraum behandelten Patienten wurden 90 von der weiteren Analyse ausgeschlossen (sekundäre Stenose eines chirurgischen Aortenklappenersatzes: 17, nur auswärtige CT-Untersuchung: 49, Tod innerhalb von 30 Tagen nach dem Eingriff: 13, mehr als milde Klappeninsuffizienz nach dem Eingriff: 10, fehlerhafte Bildarchivierung: 1). Die verbleibenden 351 Patienten bildeten das Studienkollektiv und wurden mit Klappenprothesen zweier Hersteller in unterschiedlichen Größen versorgt: 235 Patienten erhielten eine *Medtronic CoreValve* mit einer Größe von 26 mm (93 Patienten), 29 mm (135 mm) oder 31 mm (7 Patienten), bei 116 Patienten kam eine *Edward Sapien XT* mit 23 mm (38 Patienten), 26 mm (72 Patienten) oder 29 mm (6 Patienten) Durchmesser zum Einsatz. Die Auswahl der Prothesengröße oblag dem den Eingriff durchführenden Kardiologen und basierte zunächst auf den aus den vorangegangenen Untersuchungen inklusive der Echokardiographie und der Computertomographie abgeleiteten Informationen über Größe und Beschaffenheit der Aortenklappe des jeweiligen Patienten, wobei die endgültige Größenentscheidung mittels eines Ballonkatheters vorgenommen wurde. Nach der Prothesenimplantation wurde der Grad der postinterventionellen Klappeninsuffizienz mittels konventioneller Angiographie auf einer dreistufigen Likertskala abgeschätzt.

Bei allen Patienten wurde frühestens drei Monate vor dem perkutanen Klappenersatz eine kontrastangehobene EKG-getriggerte CT-Untersuchung des Herzens und der arteriellen Gefäße

des Rumpfes einschließlich der proximalen Femoralarterien durchgeführt, wobei hierfür ein Dual-Source-Gerät der ersten (Siemens Somatom Definition, 49 Patienten) oder zweiten Generation (Siemens Somatom Definition Flash, 302 Patienten) verwendet wurde. Die Kollimation betrug entweder 2 x 64 x 0,6 mm (erste Generation) oder 2 x 128 x 0,6 mm (zweite Generation), die Röhrenspannung abhängig vom Patientengewicht 100 oder 120 Kilovolt und das effektive Stromfluss-Zeit-Produkt 350-400 Milliampère/Sekunde. Alle Patienten erhielten 90 ml eines jodhaltigen Kontrastmittels über einen peripheren intravenösen Gefäßzugang mit einer Flussgeschwindigkeit von 4 ml/s.

Die so akquirierten Datensätze wurden retrospektiv von zwei erfahrenen Untersuchern unabhängig voneinander ausgewertet. Diese bestimmten die lange und kurze Achse ebenso wie den Umfang und die Fläche des Aortenannulus, wobei sich eine hohe Übereinstimmung der Messwerte beider Untersucher zeigte (Intraklassen-Korrelations-Koeffizient 0,86-0,93). Des Weiteren wurden die Mittelwerte der von beiden Untersuchern ermittelten Messwerte für den mittleren (Durchschnitt aus langer und kurzer Achse) sowie den aus dem Umfang und der Fläche abgeleiteten Diameter des Aortenannulus herangezogen, um mittels multivariater ROC-Analyse Schwellenwerte für die verschiedenen Größen beider Prothesentypen zu berechnen. Die Anwendung dieser Schwellenwerte lässt die korrekte Vorhersage der verwendeten Prothesengröße in 81,5% (Annulusumfang), 85,5% (Annulusfläche) bzw. 82,9% (mittlerer Diameter aus langer und kurzer Achse) zu. Somit konnte gezeigt werden, dass mittels der Computertomographie die Vorhersage der im Rahmen der Implantation als optimal erachteten Prothesengröße in einem Großteil aller Fälle möglich ist.

In diesem Teil der Promotionsarbeit bestand die eigene Tätigkeit in der Mitarbeit an der Konzeption des Studiendesigns, Durchführung der Messungen, Datenanalyse und Verfassen des Manuskripts.

1.4.2 Austauschbarkeit der halbautomatischen und der manuellen Vermessung des Aortenannulus in der CT vor perkutanem Aortenklappenersatz

Im Rahmen der zweiten wissenschaftlichen Arbeit wurden die CT-Datensätze eines Teils des bereits im ersten Projekt ausgewerteten Patientenkollektivs weiteren Analysen unterzogen. Von insgesamt 374 Patienten, die zwischen November 2007 und Juni 2012 am Klinikum der Universität München eine CT-Untersuchung vor geplantem perkutanem Aortenklappenersatz erhalten hatten, wurden 19 Patienten ausgeschlossen (CT-Untersuchung ohne EKG-Synchronisation: 9 Patienten, unzureichende Bildqualität: 9 Patienten, großes subvalvuläres Aneurysma mit fehlender halbautomatischer Auswertbarkeit: 1 Patient), sodass das Studienkollektiv aus 355 Patienten bestand.

Zwei erfahrene Untersucher bestimmten unabhängig voneinander neben der bereits beschriebenen Vermessung des Aortenannulus die Abstände der Koronarabgänge zur Annulusebene und schätzten zudem semiquantitativ die subjektive Bildqualität auf einer fünfstufigen sowie den Grad der Klappenverkalkung auf einer dreistufigen Likertskala ab. Einer von beiden Untersuchern ermittelte zudem das Signal-zu-Rausch-Verhältnis in der Aorta ascendens als Maß für die objektive Bildqualität. Unabhängig hiervon bestimmte ein dritter Untersucher halbautomatisch die Dimensionen des Aortenannulus sowie den Abstand der Koronarabgänge von der Annulusebene mittels einer entsprechenden kommerziell erhältlichen Software („Valve Pilot“ im „CT Cardiac Function“ Workflow, Siemens Syngo Via VA 20). Hierbei werden die Annulusebene und -kontur

durch die Software automatisch detektiert und können wenn nötig angepasst werden. Zudem wurde basierend auf der Annulusfläche eine Größenempfehlung für eine hypothetische Klappenprothese (*Edward Sapien* XT) anhand eines in der Literatur vorgeschlagenen Algorithmus abgegeben [40]. Bei unterschiedlichen Größenempfehlungen für diese Klappenprothese zwischen beiden manuellen oder zwischen der manuellen und der halbautomatischen Annulusvermessung wurde die zugrundliegende Differenz der Annulusfläche als mild (weniger als 5%), moderat (5-10%) oder schwer (mehr als 10%) klassifiziert.

Während der halbautomatischen Vermessung war in 11% der Fälle eine Korrektur der automatisch vorgeschlagenen Annulusebene notwendig, wohingegen in 10% der Fälle keinerlei Änderung der von der Software vorgeschlagenen Vermessung notwendig war. In den restlichen Fällen wurde eine Korrektur der Annuluskontur ohne Änderung der Ebene vorgenommen. Die so erzielten Messergebnisse zeigten eine hohe Übereinstimmung mit der manuellen Vermessung (Intraklassen-Korrelations-Koeffizienten 0,86-0,95), ähnlich der Übereinstimmung der manuellen Messwerte der beiden unabhängigen Untersucher (Intraklassen-Korrelations-Koeffizienten 0,89-0,94). Zudem wurden zwischen der halbautomatischen und der manuellen Evaluation keine statistisch signifikanten Unterschiede zwischen Subgruppen mit unterschiedlicher subjektiver oder objektiver Bildqualität und unterschiedlicher Kalklast gefunden. Hinsichtlich der vorgeschlagenen Klappengröße stimmten beide Untersucher in 81% aller Fälle überein, wobei die zugrundeliegende Differenz der Annulusfläche bei verschiedenen Klappenempfehlungen in 35% als mild, in 44% als moderat und in 21% als schwer klassifiziert wurde. Ähnliche Übereinstimmungswerte wurden zwischen der manuellen und der halbautomatischen Vermessung beobachtet: So wurde in 82% der Fälle die gleiche Klappengröße vorgeschlagen, die zugrundeliegende Differenz der Annulusfläche bei verschiedenen Klappenempfehlungen wurde in 40% als mild, in 38,5% als moderat und in 21,5% als schwer eingestuft. Somit konnte gezeigt werden, dass die halbautomatische Evaluation

des Aortenannulus in CT-Untersuchungen vor perkutanem Aortenklappenersatz unabhängig von der Bildqualität und dem Grad der Klappenverkalkung gleichwertige Ergebnisse zur manuellen Evaluation durch erfahrene Untersucher liefert, was auch in einer vergleichbaren Größenempfehlung für eine Aortenklappenprothese Ausdruck findet.

Der eigene Beitrag bestand in diesem Teil der Promotionsarbeit aus Mitarbeit bei der Durchführung der Messungen, der Datenanalyse und dem Verfassen des Manuskripts.

1.5 Zusammenfassung und Ausblick

Der perkutane Aortenklappenersatz hat sich seit seiner Einführung von einer zunächst experimentellen zur Standardtherapie der schweren Aortenstenose bei solchen Patienten entwickelt, denen ein Klappenersatz zuvor aufgrund des als zu hoch erachteten operativen Risikos verwehrt blieb. Daneben werden inzwischen auch Patienten mit intermediärem Operationsrisiko auf diese Weise behandelt, sodass trotz für dieses Patientenkollektiv noch ausstehender Langzeitergebnisse zukünftig von einer weiteren Zunahme der weltweit durchgeführten Eingriffe auszugehen ist. Die Computertomographie hat sich dabei als integraler Bestandteil der präinterventionellen Diagnostik zur Eingriffsplanung etabliert, wobei die vorliegende Arbeit zwei Aspekte der CT-basierten Größenbestimmung der Klappenprothese vor perkutanem Aortenklappenersatz herausarbeitet.

Angesichts dieser erfolgreichen Bilanz ist inzwischen die Mitralinsuffizienz als zweithäufigster Klappenfehler in den Fokus der interventionellen Therapie gerückt, da auch hier viele Patienten mit behandlungswürdigem Vitium aufgrund des zu hohen Risikos nicht für einen operativen Klappenersatz in Frage kommen [57, 58]. Auch beim perkutanen Mitralklappenersatz sind bildgebende Methoden inklusive der Computertomographie zur Eingriffsplanung unerlässlich [59,

60]. Da die Entwicklung des perkutanen Mitralklappenersatzes noch voranschreitet und die Bedeutung der Computertomographie in diesem Kontext Gegenstand aktueller Forschung ist [61], bleibt abzuwarten, ob dieser Intervention auch aus radiologischer Sicht zukünftig eine ähnlich große Rolle zukommen wird wie dem perkutanen Aortenklappenersatz.

1.6 Zusammenfassung der vorliegenden Arbeiten

Die Aortenstenose ist die häufigste Erkrankung der Herzklappen und tritt in erster Linie bei älteren Patienten auf. Da die Erkrankung nach der Entwicklung von Symptomen eine schlechte Prognose hat und keine effektiven pharmakologischen Behandlungsansätze zur Verfügung stehen, stellt der Ersatz der Aortenklappe die einzige kurative Behandlungsoption dar. Der hierfür als Goldstandard geltende chirurgische Klappenersatz ist jedoch bei einem beträchtlichen Anteil der betroffenen, häufig multimorbiden Patienten aufgrund des als zu hoch erachteten perioperativen Risikos nicht möglich. Als Alternative hat sich daher der kathetergestützte perkutane Aortenklappenersatz etabliert, der inzwischen auch bei Patienten mit intermediärem Operationsrisiko durchgeführt wird.

Im Gegensatz zum chirurgischen Aortenklappenersatz geht dem perkutanen Klappenersatz eine gründliche Evaluation der Aortenklappe mittels bildgebenden Methoden voraus, um die optimale Größe der Klappenprothese zu bestimmen. Aufgrund ihrer hohen räumlichen Auflösung mit dreidimensionaler Abbildung der komplexen Anatomie der Aortenwurzel und der kompletten Darstellung des vaskulären Zugangswegs leistet die Computertomographie hierfür einen entscheidenden Beitrag. Das Ziel der vorliegenden Dissertationsschrift war es, zwei Aspekte der CT-basierten Größenbestimmung der Klappenprothese vor perkutanem Aortenklappenersatz zu beleuchten.

Die erste wissenschaftliche Arbeit untersuchte retrospektiv, inwiefern sich die Computertomographie dazu eignet, die optimale Größe einer perkutan eingebrachten Aortenklappenprothese anhand der vor dem Eingriff akquirierten Bilder vorherzusagen. Hier konnte gezeigt werden, dass die korrekte Vorhersage der Klappengröße in mehr als 85% aller Fälle möglich ist. Zudem wurden Schwellenwerte für die Größe des Aortenannulus für unterschiedliche Typen und Größen von perkutanen Klappenprothesen berechnet.

Das zweite wissenschaftliche Projekt ging der Frage nach, ob sich die Verwendung einer Software zur halbautomatischen Vermessung ebenso gut zur Evaluation des Aortenannulus eignet wie die manuelle Vermessung durch erfahrene Untersucher. Hier zeigte sich, dass die halbautomatische Auswertung unabhängig von der subjektiven und objektiven Bildqualität und dem Ausmaß der Klappenverkalkung zur manuellen Messung gleichwertige Ergebnisse liefert, die sich folgerichtig auch in vergleichbaren Empfehlungen für die Größe der zu implantierenden Prothese widerspiegeln.

1.7 Summary of the presented publications

Aortic stenosis is the most common cardiac valve disorder and mostly affects elderly patients. In its symptomatic form, the prognosis is poor. Currently, there is no effective medical treatment. Therefore, replacement of the aortic valve is the only curative treatment option, with surgical aortic valve replacement being the gold standard. However, many of the affected patients are denied surgery because the perioperative risk is deemed too high due to comorbidities. Trans-catheter aortic valve replacement (TAVR) has been developed as a less-invasive alternative in these patients. Meanwhile, its application has been widened to individuals with intermediate perioperative risk.

Contrary to surgical valve replacement, an imaging-based rigorous evaluation of the aortic root is necessary prior to TAVR, to obtain optimal sizing of the prosthesis. With its capability to depict the complex three-dimensional anatomy of the aortic root and the vascular access route with high spatial resolution, computed tomography plays a key role in the work-up of these patients. This thesis aimed to highlight two different facets of CT-based prothesis sizing prior to TAVR.

The first scientific work retrospectively investigated if computed tomography is suited to predict optimal prothesis size in TAVR based on the analysis of the CT datasets acquired prior to the procedure, which turned out to be possible in more than 85% of cases. Furthermore, cut-off values of the aortic annulus size for different types and sizes of trans-catheter aortic heart valves were provided.

The second scientific project compared software-based semiautomatic evaluation of the aortic annulus to full manual measurements by experienced observers. It was shown that the measurements obtained by semiautomatic evaluation are interchangeable with full manual measurements independent of subjective and objective image quality or degree of calcification of the aortic leaflets, which results in similar recommendations concerning prothesis size.

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2. Ergebnisse

2.1. CT-angiography-based evaluation of the aortic annulus for prosthesis sizing in transcatheter aortic valve implantation (TAVI)-predictive value and optimal thresholds for major anatomic parameters.

Schwarz F, Lange P, **Zinsser D**, Greif M, Boekstegers P, Schmitz C, Reiser MF, Kupatt C, Becker HC

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CT-Angiography–Based Evaluation of the Aortic Annulus for Prosthesis Sizing in Transcatheter Aortic Valve Implantation (TAVI)–Predictive Value and Optimal Thresholds for Major Anatomic Parameters

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Abstract

Background/Objectives: To evaluate the predictive value of CT-derived measurements of the aortic annulus for prosthesis sizing in transcatheter aortic valve implantation (TAVI) and to calculate optimal cutoff values for the selection of various prosthesis sizes.

Methods: The local IRB waived approval for this single-center retrospective analysis. Of 441 consecutive TAVI-patients, 90 were excluded (death within 30 days: 13; more than mild aortic regurgitation: 10; other reasons: 67). In the remaining 351 patients, the CoreValve (Medtronic) and the Edwards Sapien XT valve (Edwards Lifesciences) were implanted in 235 and 116 patients. Optimal prosthesis size was determined during TAVI by inflation of a balloon catheter at the aortic annulus. All patients had undergone CT-angiography of the heart or body trunk prior to TAVI. Using these datasets, the diameter of the long and short axis as well as the circumference and the area of the aortic annulus were measured. Multi-Class Receiver-Operator-Curve analyses were used to determine the predictive value of all variables and to define optimal cutoff-values.

Results: Differences between patients who underwent implantation of the small, medium or large prosthesis were significant for all except the large vs. medium CoreValve (all $p's<0.05$). Furthermore, mean diameter, annulus area and circumference had equally high predictive value for prosthesis size for both manufacturers (multi-class AUC's: 0.80, 0.88, 0.91, 0.88, 0.88, 0.89). Using the calculated optimal cutoff-values, prosthesis size is predicted correctly in 85% of cases.

Conclusion: CT-based aortic root measurements permit excellent prediction of the prosthesis size considered optimal during TAVI.

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Introduction

Aortic valve stenosis is the most common acquired valve disorder and symptomatic forms have dismal outcomes when treated medically [1,2]. For decades, surgical valve replacement has been the only curative treatment – however, due to comorbidities at the time of presentation up to one third of patients cannot undergo open heart surgery [3–5]. Transcatheter Aortic Valve Implantation (TAVI)/Transcatheter Aortic Valve Replacement (TAVR) is a novel, less invasive technique and is comparably safe even in patients with contraindications to surgery [6,7]. Results of the randomized controlled PARTNER-B-cohort comparing TAVI to best medical therapy have shown substantial survival benefits after 12 and 24 months [8,9]. In patients with a high surgical risk (PARTNER-A-cohort), TAVI was non-inferior to surgery after 12 months [10].

Unlike in surgical replacement, prosthesis sizing for TAVI significantly relies on imaging [11]. Imaging-derived measurements of the aortic root play the key role in patient and device selection. Transesophageal echocardiography and Multidetector

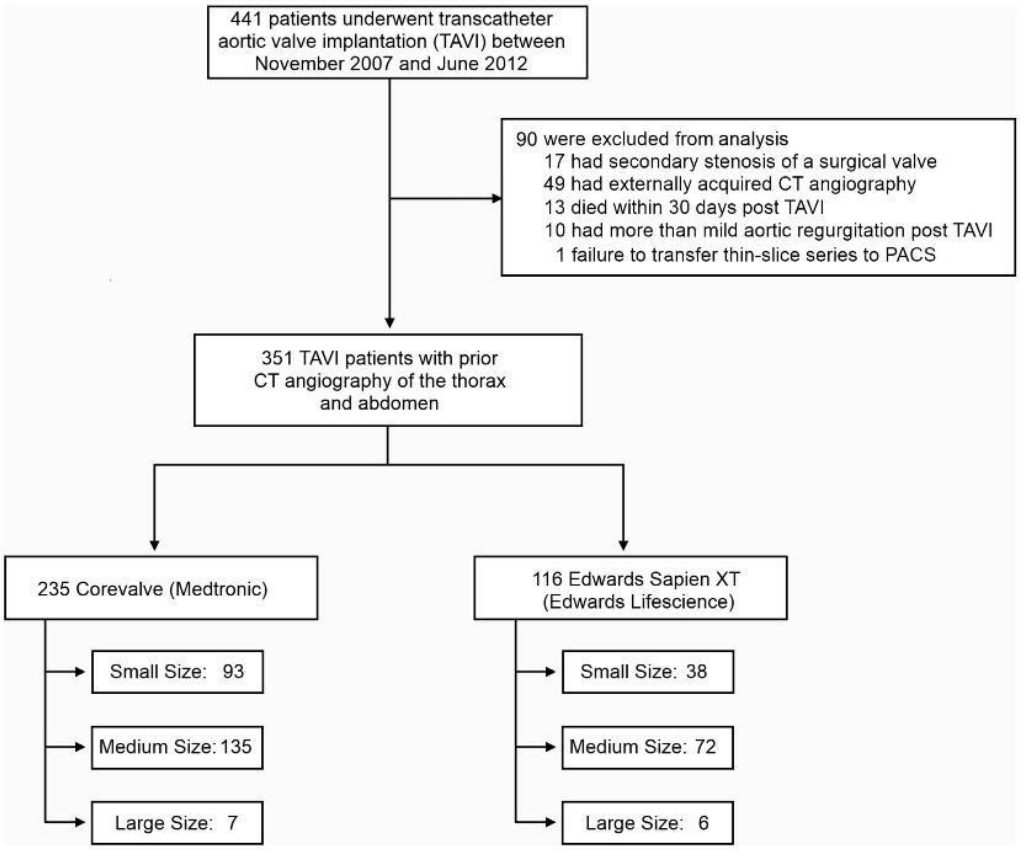

Figure 1. Inclusion chart for our analysis of 351 patients who underwent a successful TAVI procedure.
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CT-angiography (CTA) have been applied extensively in this regard [12–14]. Several studies have consistently demonstrated that the aortic annulus has an elliptic shape described by a long and short axis with a wide range of reported eccentricities [15,16]. As a consequence, it is difficult to measure the true dimensions of the aortic annulus on the basis of a single plane obtained by 2D-echocardiography [17,18].

There is initial evidence favoring CTA over echocardiography for prosthesis selection. Recently, Jilaihawi et al had demonstrated for the SAPIEN XT valve (Edwards Lifesciences) that annular-sizing on the basis of CT resulted in lower rates of paravalvular regurgitation than sizing on the basis of 2D TEE [17]. Similar results had previously been reported by Hayashida et al for patients having undergone implantation of the Corevalve (Medtronic) or Sapien XT valve (Edwards Lifesciences) [19].

Several questions remain as to how select the optimal prosthesis size on the basis of CT-derived annulus parameters and most authors use a fixed algorithm suggesting certain annulus diameter ranges for distinct prosthesis sizes. Recently, Binder et al reported that the application of a CT-based annulus area sizing algorithm prior to TAVI resulted in the reduction of paravalvular regurgitation compared with simply providing quantitative results for anatomical parameters [20].

In this study, we analyzed all patients (n = 351) who had undergone dedicated CT-angiography prior to TAVI at our institution. We report descriptive statistics for the key anatomic parameters of the aortic root, determine interobserver reproducibility for CT-derived measurements and analyze various anatomic variables for their predictive value for the selection of optimal device size. Suggestions are provided for optimal cutoff values for CT-based measurements.

Methods

1. Patient Population

This analysis included patients with severe aortic valve stenosis who underwent a TAVI procedure at our institution between November 2007 and June 2012. Patients needed to have undergone CTA for the evaluation of aortic root anatomy within three months before TAVI. As all CT scans were performed as part of routine clinical workup and were analyzed anonymously,

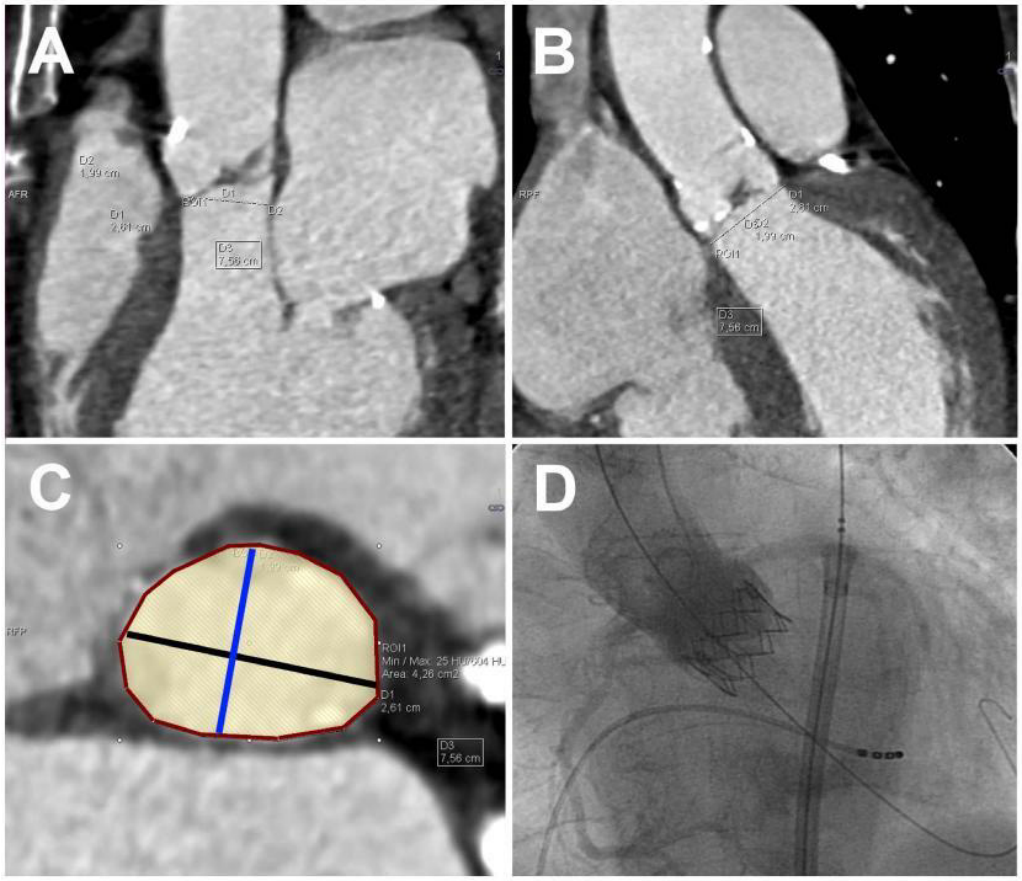

Figure 2. Examples of anatomic measurements at the aortic annulus performed for this study: isotropic small field-of-view CTA dataset of a 78 year old female patient with severe aortic stenosis, A) sagittal reformation and B) coronal reformation showing the orientation of the aortic annulus plane, C) double-oblique reformation of the aortic valve annulus, demonstrating the diameter of the long axis (black line), the diameter of the short axis (blue line), the annulus circumference (red polygonal), and annulus area (yellow shading). D) angiographic image after implantation of a 26 mm model of the Edward Sapien XT valve prosthesis demonstrates no paravalvular leakage.
doi:10.1371/journal.pone.0103481.g002

the institutional review board of the Faculty of Medicine of the Ludwig Maximilian University of Munich waived the necessity to obtain consent beyond routine clinical requirements. All patients gave written consent to an anonymous analysis of the acquired data.

According to institutional policies patients with impaired renal function (glomerular filtration rate <30 ml/min), abnormal TSH-levels or a history of allergic reaction to iodine-containing contrast agents were excluded. After explicit education about the risks of iodinated contrast agents and exposure to x-rays, written informed consent was obtained (Figure 1).

2. CT Data Acquisition and Image Reconstruction

CT scans were performed either on a first-generation dual-source MDCT scanner (n = 49, Somatom Definition, Siemens Healthcare, Forchheim, Germany) or on a second-generation dual-source MDCT scanner (n = 302, Somatom Definition Flash, Siemens Healthcare) 3–90 days before TAVI. The ECG-signal was registered continuously throughout the scan. Images of the heart were acquired during diastole. Slice collimation was 2×64×0.6 mm (first generation) or 2×128×0.6 mm (second generation). Tube potential was 100 or 120 kV (depending on patient weight) and effective tube current-time product was 350–400 mAs/rotation. See Appendix S1 for detailed scan parameters.

In all patients, 90 ml of iomeprol 816.5 g/l (Imeron 400, Bracco Imaging, Milan, Italy) were administered via an ante-cubital vein at a flow-rate of 4 ml/s, followed by 100 ml of normal saline at the same flow rate. Contrast enhancement was controlled by bolus tracking within the ascending aorta.

Table 1. Patient parameters, N(%), mean ± SD or median [interquartile range] and summary of implanted valve sizes.

	All Patients	CoreValve Subgroup	Edward Sapien Subgroup	p
n	351 (100%)	235 (67%)	116 (33%)	
Female Patients	211 (58%)	132 (54%)	74 (62%)	0.18
Age at scan (yrs)	80.9±10.8	81.6±6.5	76.3±21.5	0.06
Height (cm)	165.7±8.9	165.5±13.9	163.2±18.2	0.125
Weight (kg)	72.9±14.7	72.6±15.0	72.1±17.0	0.83
BMI (kg/m^2)	26.5±4.8	26.3±4.5	26.8±5.4	0.62
Aortic Valve Area (cm^2)	0.70±0.15	0.69±0.16	0.72±0.13	0.21
Pressure gradient (mmHg)	66.9±22.4	67.3±23.8	66.0±19.6	0.65
Ejection fraction (%)	58.0±15.3	57.8±16.0	58.3±13.6	0.80
Logistic EuroSCORE	18.9 [13.4; 25.7]	19.6 [14.5; 26.7]	16.5 [11.0; 23.4]	<0.01
Valve Sizes:				
Small Size	131 (37%)	93 (40%)	38 (33%)	0.25
Medium Size	207 (59%)	135 (57%)	72 (62%)	0.44
Large Size	13 (4%)	7 (3%)	6 (5%)	0.52

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Once intraluminal attenuation exceeded 150 HU, the table was repositioned for the desired scan range. Delay was 6 seconds (Somatom Definition) or 12 seconds (Somatom Definition Flash). Thereafter, the start of the scan was triggered by ECG automatically.

A medium-smooth convolution kernel was used to generate standard coronary CTA reconstructions (small field of view, slice thickness 0.75 mm, reconstruction increment 0.5 mm covering the entire heart). All series were pseudonymized and transferred to an external workstation.

3. CT Data Analysis

Two experienced readers analyzed all series independently using commercially available software (Syngo Via VA20, Siemens Healthcare, Germany). Readers determined subjective image quality and contrast enhancement on 4-point Likert scales (4: best image quality/contrast enhancement, 1: poor image quality/contrast enhancement). Furthermore, both readers measured the size of the aortic annulus according to techniques suggested by various authors [12,21–23]. Using multiplanar reformations, readers independently established the double-oblique plane defined by the three 'hinge' points (i.e. the most apical points of the valvular cusps, see Figure 2). On this plane, both readers manually determined the lengths of the long axis (LA), short axis (SA), circumference (C) and area (A) of the elliptical shape of the the aortic valve annulus (Figure 2). Three virtual diameters (d_{mean}, d_C *and* d_A) were derived from these parameters according to the following formulae:

$$d_{mean} = \frac{LA + SA}{2};\ d_C = \frac{C}{\pi};\ d_A = 2 \times \sqrt{\frac{A}{\pi}}$$

4. Clinical and procedural data

In all patients, TAVI was performed at the department of cardiology of this institution as part of routine clinical care. Patients were admitted at least 1 day prior to TAVI and transferred to a high-level intensive care unit for at least 24 hours afterwards. All patients underwent a routine transthoracic echocardiography exam within 7 days prior to TAVI.

Selection of valve type (CoreValve by Medtronic, Minneapolis, USA vs. Edward Sapien XT by Edwards Lifesciences, Irvine, CA, USA) and size was performed by the heart team members before and during TAVI. According to the standard operating procedures of this institution, an initial estimation of annulus size was performed based on all available imaging information. During the procedure, a balloon catheter with the estimated size was inflated at the annulus position and snug fit was evaluated by fluoroscopy and balloon pressures [24–26]. Depending on the appearance of the balloon and the recorded pressures, valve size was either confirmed or changed. In the latter case, a different balloon catheter was used and the changed size tested. Once optimal size had been established, the respective valve was implanted using the techniques recommended by manufacturers. Thereafter, conventional angiography was performed to test for aortic regurgitation, which was rated on a three point Likert scale (1: no, minimal or first degree regurgitation, 2: second degree regurgitation, 3: severe regurgitation).

5. Statistical Analysis

The D'Agostino-Pearson test was used to test for normal distribution of continuous variables. Continuous variables are reported as mean ± standard deviation when normally distributed, otherwise as median (interquartile range).

For categorical variables, Cohen's kappa was used to address observer agreement and was reported with 95% confidence interval. For continuous variables, the intraclass correlation coefficient (ICC) was used [27].

Differences in proportions were assessed using the Chi-squared test. To test for differences in means of interval variables, the Student's t-test (for independent or paired samples) was applied if variables followed normal distribution. For comparison of means of three or more variables, a one-way analysis of variance (ANOVA) was performed. If significant differences were found, variables were compared using the Tukey-HSD post-hoc test with

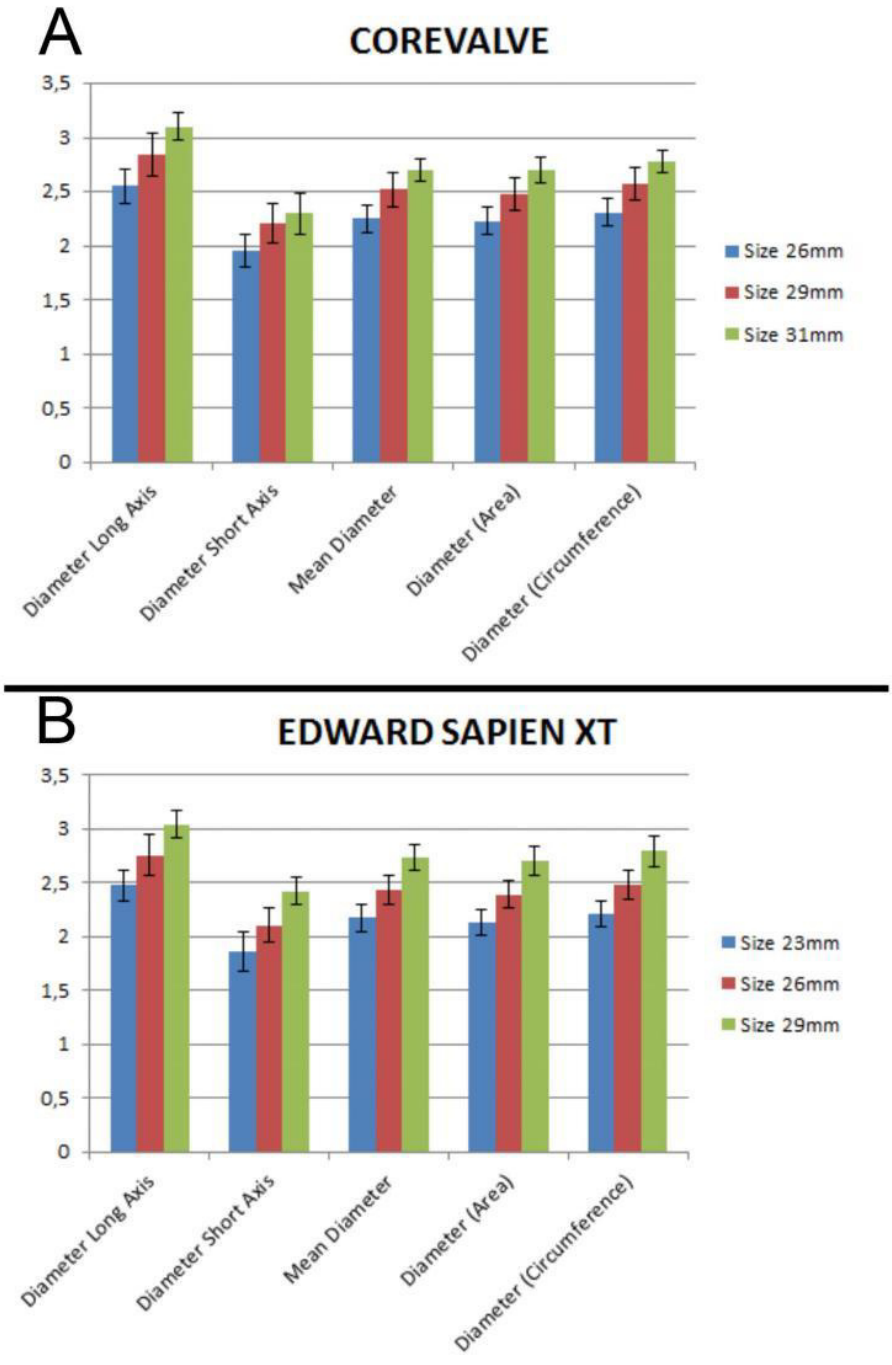
A
COREVALVE
3,5
3
2,5
2
1,5
1
0,5
0
Size 26mm
Size 29mm
Size 31mm
Diameter Long Axis
Diameter Short Axis
Mean Diameter
Diameter (Area)
Diameter (Circumference)
B
EDWARD SAPIEN XT
3,5
3
2,5
2
1,5
1
0,5
0
Size 23mm
Size 26mm
Size 29mm
Diameter Long Axis
Diameter Short Axis
Mean Diameter
Diameter (Area)
Diameter (Circumference)

Figure 3. Summary chart displaying major anatomic parameters (length of long and short axis; circumference-derived and area-derived virtual diameter) in patients in whom the small, medium or large size model was considered optimal for A) the CoreValve valve and the B) Edward Sapien XT valve. Except for the large vs. medium CoreValve size, all differences were statistically significant ($p<0.05$).
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application of Bonferroni corrections to avoid errors due to multiple testing.

To compare means in variables not following normal distribution, a t-test was used if normal distribution was approximated after logarithmic transformation. In all other cases, non-parametric tests were used: the Mann-Whitney-test for independent variables and the Wilcoxon signed-rank test for paired variables.

To identify cut-off points that allow optimal prediction of implanted valve size on the basis of the particular anatomic parameter, and to estimate the associated generalization performance, we applied a 10-fold nested cross-validation approach. Details regarding this approach are included in Appendix S1.

P-values of 0.05 or less were considered statistically significant unless otherwise stated. Data were analyzed using MedCalc (Version 9.3.0.0, MedCalc Software, Mariakerke, Belgium), SPSS (21.0, IBM, Armonk, USA) and R [28].

Results

1. Patient Population

Between November 2007 and June 2012, 441 consecutive patients with high-grade aortic stenosis (mean AVA: 0.70 cm^2, SD: 0.15 cm^2) underwent a TAVI procedure at our institution. Of these, 17 patients were excluded as they presented with secondary stenosis of a surgical aortic valve prosthesis. Another 49 patients presented with externally acquired CT angiography datasets and were also excluded from this analysis. Of the remaining patients, 13 had died within 30 days after procedure and were not included into further analysis. 10 patients were excluded as they showed more than mild aortic regurgitation after valve implantation. Finally, one patient was excluded due to an error during archiving the small FOV (cardiac) series to PACS (Figure 1).

Of the remaining 351 patients, 235 had undergone implantation of a CoreValve prosthesis while in the remaining 116 patients the Edwards Sapien XT valve had been implanted. While differences in demographic parameters and preinterventional echocardiographic parameters between patients who underwent CoreValve vs. Edward Sapien XT valve implantation were not statistically significant, there was a difference in logarithmic EuroScores (19.6 [14.5; 26.7] vs. 16.5 [11.0; 23.4], $p<0.01$, see Table 1 for a summary of patient parameters) demonstrating a moderately less favorable risk profile in the CoreValve subgroup. In the entire cohort, no adverse events due to iv contrast administration during CT angiography were reported.

2. Subjective image quality and contrast enhancement of CTA datasets

There was substantial interobserver agreement for both subjective overall image quality (kappa = 0.76 [0.69–0.82]) and contrast enhancement (kappa = 0.72 [0.67–0.77]). Therefore, values from reader one were used for further analysis. Mean subjective image quality was 3.66 (SD: 0.58) and mean contrast enhancement was 3.88 (SD: 0.43).

3. CT-based anatomical measures of the aortic root

Interobserver agreement was excellent for all parameters with ICC-values consistently above 0.80. Bland-Altman-Analysis revealed no relevant systematic differences (Table 2 and Appendix S2). Therefore, arithmetic means between both observers were calculated for all variables.

Table 3 provides descriptive statistics on aortic valve measurements. Across all patients, length of the long axis and short axis were 2.70 [2.52; 2.90] and 2.05 [1.95; 2.25], respectively, and were slightly larger in the CoreValve subgroup than in the Edward Sapien subgroup (see Table 3). Median circumferences and median areas were 7.65 [7.28; 8.15] cm and 4.34 [3.90; 4.95] cm^2. There was a small but significant difference in average annulus diameters derived from circumference (2.44 [2.32; 2.60] cm) vs. those derived from annulus area (2.35 [2.23; 2.51] cm, $p<0.01$).

4. Annulus dimensions for different valve sizes

Of the 235 patients who underwent implantation of a CoreValve prosthesis, the 26 mm, 29 mm and 31 mm models were chosen in 93 (40%, 93/235), 135 (57%, 135/235) and 7 (3%, 7/235) cases. In 116 patients who received the Edward Sapien XT valve, the 23 mm, 26 mm and 29 mm were implanted in 38 (33%, 38/116), 72 (62%, 72/116) and 6 (5%, 6/118) cases.

Figure 3 provides details on long axis diameter, short axis diameter, circumference-derived and area-derived average annulus diameter measured for different sizes of CoreValve (Figure 3A) and Edward Sapien XT (Figure 3B). For all analyzed variables, one-way ANOVA showed significant differences between patients who underwent implantation of the small, middle or large valve (for the CoreValve: 26 mm, 29 mm, 31 mm; for the Edward Sapien XT: 23 mm, 26 mm, 29 mm, both p's<0.01). In Tukey-HSD post-hoc tests, differences between all size subgroups were statistically significant except for patients who underwent implantation of the CoreValve 31 mm vs. 29 mm ($p>0.05$), which was most likely due to the relatively small number of patients in the 31 mm CoreValve subgroup (n = 7).

Table 2. Interobserver Agreement for anatomical measurements of the aortic root reported as Intraclass Correlation Coefficient (ICC) and parameters of Bland-Altman-Analysis.

	Diameter long axis	Diameter short axis	$Diameter_{Mean}$	Annulus Circum-ference	Annulus Area
ICC [95% CI]	0.87 [0.84; 0.89]	0.86 [0.83; 0.88]	0.90 [0.88; 0.92]	0.92 [0.90; 0.93]	0.93 [0.92; 0.94]
Mean difference	0.00 cm	0.00 cm	0.00 cm	0.06 cm	0.03 cm^2
SD of differences	0.14 cm	0.12 cm	0.20 cm	0.54 cm	0.6 cm^2

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Table 3. Primary anatomic parameters of the aortic annulus, N(%), mean ± SD or median [interquartile range] as well as "virtual diameters" derived from the mean of long axis and short axis, from annulus circumference and annulus area.

	All Patients	CoreValve Subgroup	Edward Sapien Subgroup	p
Diameter Long Axis [cm]	2.70 [2.52; 2.90]	2.75 [2.54; 2.90]	2.65 [2.50; 2.85]	0.049
Diameter Short Axis [cm]	2.05 [1.95; 2.25]	2.10 [1.95; 2.28]	2.05 [1.90; 2.20]	<0.01
Circumference [cm]	7.65 [7.28; 8.15]	7.73 [7.30; 8.25]	7.55 [7.05; 8.00]	<0.01
Area [cm^2]	4.34 [3.90; 4.95]	4.44 [3.98; 5.05]	4.19 [3.70; 4.75]	<0.01
$Diameter_{Mean}$ [cm]	2.40 [2.25; 2.55]	2.42 [2.27; 2.58]	2.35 [2.22; 2.52]	<0.01
Circumference- derived virtual diameter [cm]	2.44 [2.32; 2.60]	2.46 [2.32; 2.63]	2.40 [2.24; 2.55]	<0.01
Area-derived virtual diameter [cm]	2.35 [2.23; 2.51]	2.38 [2.25; 2.54]	2.31 [2.17; 2.46]	<0.01

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5. Predictive value of different variables for device size selection and optimal cutoff values

Using multi-class ROC-analysis, the predictive value of all anatomic parameters for the size of prosthesis considered optimal was evaluated. For both valve types, all five analyzed parameters showed high predictive value for optimal prosthesis size (AUC: 0.75–0.91, Table 4). In particular, for the Medtronic CoreValve the short axis had a somewhat lower predictive value (multi-class AUC: 0.75) while there were no differences in predictive value between diameters of long axis, mean diameter, annulus area or annulus circumference (multi-class AUC's: 0.81, 0.80, 0.88, 0.9, $p>0.05$, Appendix S3). For the Edwards Sapien XT valve, differences in predictive value between the different parameters also did not reach statistical significance (multi-class AUC's: 0.83, 0.80, 0.88, 0.88, 0.89, $p>0.05$, Appendix S4). Application of the proposed cutoff-values in our sample of 351 patients results in the correct classification of 81.5% (286/351), 85.5% (300/351) and 82.9% (291/351) of cases if annulus circumference, annulus area or mean diameter are used.

Discussion

Transcatheter aortic valve implantation (TAVI) has been developed as a treatment strategy for patients with severe aortic stenosis who are at high risk or not eligible for heart surgery [29]. Several studies have demonstrated that MDCT is an ideal imaging modality prior to TAVI, providing isotropic datasets of the aortic root that can be reformatted in any spatial orientation [30–32]. There is some evidence favoring CT-derived annulus sizing over transthoracic echocardiography, particularly in regard to the incidence of postinterventional aortic regurgitation [17,19].

Several methods have been proposed to reduce the shape of the aortic annulus to a single measure for prosthesis sizing: calculation of the arithmetic mean between long and short axis [21], measurement of the length of the annulus circumference [12] or quantification of the annulus area [22,23]. To date, no consensus has been established on what the best technique is.

Binder et al have recently demonstrated for the Sapien XT valve that the recommendation of a particular prosthesis size on the basis of CT data results in more favorable outcomes than simply providing the annulus parameters [20]. In this regard

Table 4. Multi-Class AUC's as measures for the predictive value of the respective anatomic parameters for the valve size considered optimal by the implantation team.

	PARAMETER	OPTIMAL CUTOFF SMALL vs. MEDIUM	OPTIMAL CUTOFF MEDIUM vs. LARGE	MULTI-CLASS AUC
MEDTRONIC COREVALVE	Diameter Long Axis	2.70 cm	3.04 cm	0.8133
	Diameter Short Axis	2.05 cm	2.29 cm	0.7478
	$Diameter_{Mean}$	2.35 cm	2.70 cm	0.7974
	Annulus Area	4.30 cm^2	5.72 cm^2	0.8812
	Annulus Circumference	7.65 cm	8.60 cm	0.9146
EDWARDS SAPIEN XT	Diameter Long Axis	2.55 cm	3.05 cm	0.8347
	Diameter Short axis	1.95 cm	2.30 cm	0.7995
	$Diameter_{Mean}$	2.25 cm	2.55 cm	0.8793
	Annulus Area	3.85 cm^2	5.35 cm^2	0.8823
	Annulus Circumference	7.15 cm	8.20 cm	0.8884

Optimal cutoff values for the selection of the small, medium or large prosthesis size, defined as cutoff values that result in highest predictive accuracy.
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however, uncertainty remains as to what the optimal size of prosthesis is for a given set of aortic annulus parameters.

In this analysis of over 350 patients who had undergone CT angiography prior to TAVI, we performed extensive anatomic measurements of the aortic root. Our results confirm previous analyses of Halpern et al [14], Gurvitch et al [12] and Delgado et al [33], since all relevant anatomic parameters can be measured in virtually all patients with excellent agreement between two experienced observers. Similar to the study by Gurvitch, observer agreement was highest for aortic annulus circumference and area (ICC's = 0.92, 0.93), even though in our study differences to observer agreement for long and short axis measurements were not significant.

In all patients included in this analysis, optimal prosthesis size was determined with the help of a sizing balloon catheter inflated during the implantation procedure [24–26]. Furthermore, all patients in whom this method might not have resulted in the selection of the correct prosthesis size – i.e. patients with more than mild regurgitation after TAVI (n = 10) and patients who died within 30 days after implantation (n = 13) – were deliberately excluded. No patient had to be excluded due to open heart surgery within 30 days. According to best professional judgment, prosthesis sizing was adequate in the remaining 351 patients. Thus, our data permit the unique opportunity to analyze the relation between different anatomic variables of the aortic root and the device size ultimately considered optimal. Even more importantly, the discriminatory power of different anatomic variables to predict prosthesis size as well as optimal cutoff values can be calculated.

Our results demonstrate that for all analyzed anatomic variables there are differences between patients who underwent implantation of the small, medium or large valve. Our results are both in line with but also extend those of Jilaihawi et al [17] and Delgado et al [34], demonstrating that on the basis of high-resolution MDCT datasets of the aortic root, the optimal valve size can be predicted. While in principle all evaluated anatomic parameters can be used for prosthesis sizing, the most favorable combination of high observer agreement and predictive value are observed for mean diameter, annulus area and annulus circumference (with multi-class AUC's of 0.88 and 0.91). Optimal thresholds for the selection of the small, medium or large size are given in Table 4. The use of these cutoff values in our cohort results in the correction prediction of valve size in 85% (300/351) of cases. In the remaining 15% (51/351), the application of a sizing balloon would result in a change of device size. Importantly, our 2-threshold-model does not take into account that a considerable number of patients will be suitable candidates for two valve sizes. Inclusion of the extent of aortic valve calcifications might further increase the predictive accuracy of our model.

Our single-center retrospective study has several limitations: first, the heart team members involved in valve implantation were not blinded towards the routine radiological reports derived from the CT dataset. While this would have been favorable from a scientific perspective, we feel that the information obtained from high-resolution CT angiography datasets prior to TAVI is of so essential a nature that withholding it would be clearly unethical. Furthermore, cardiologists integrated all available information regarding valve size, including transthoracic and transesophageal echocardiography and aortic angiography usually conducted before the TAVI procedure. In every single case, the presumed optimal valve size was simulated with a balloon catheter and changed if the size of the inflated balloon and the aortic annulus did not display the estimated ratio during aortography.

Second, we did not compare our measurements with a reference imaging modality such as 3D-echocardiography or MR angiography. However, our reference standard is the size of the implanted valve in those patients in whom – according to best professional judgment – prosthesis size turned out to be reasonably selected. For the purpose of this analysis we consider this outcome-oriented reference standard superior.

Third, we used only diastolic CT acquisitions to measure aortic annulus dimensions. However, it still is a matter of debate if systolic reconstructions are necessary for a reliable sizing of the aortic valve annulus: while some authors propose systolic reconstructions to avoid undersizing [35,36], others report no difference [37] or no substantial difference [38] between systolic and diastolic diameters. However, since we correlate our diastolic measures of annulus parameters with the prosthesis size considered optimal during implantation, a potential difference between systolic and diastolic dimensions is not a major concern; our results should rather be construed as a contribution to a prosthesis sizing algorithm from diastolic annulus parameters.

Fourth, we do not perform an analysis of the patients in whom valve implantation was not successful. However, the main intention of our manuscript is to perform a rigorous analysis of the dependencies between anatomical parameters of the aortic annulus and the implanted valve size for patients in whom the procedure was performed successfully. In that sense, we do not attempt to prove that an inadequate selection of prosthesis size increases the risk of a negative procedural outcome.

Finally, while our analysis suggests an ideal strategy to predict the appropriate valve size, we cannot answer the question how this strategy would perform in a prospective study context. However, the rate of excluded patients is comparatively small: only 23 patients had to be excluded due to either death within 30 days after the TAVI procedure (n = 13) or due to the development of more than mild aortic regurgitation (n = 10). Therefore, we are confident that our approach would permit a correct estimation of correct valve size in the vast majority of cases.

In conclusion, our analysis of 351 patients who successfully underwent TAVI shows that the valve size ultimately considered optimal can be predicted on the basis of CT-derived anatomic parameters of the aortic root. Mean diameter, annulus circumference and annulus area appear to have equally high reproducibility and predictive accuracy for both the Medtronic CoreValve and the Edwards Sapien XT prostheses. It remains to be shown that this approach holds up its predictive potential in a prospective study context.

Supporting Information

Appendix S1 Supplemental methods section including details on CT data acquisition, image reconstruction and statistical methods.
(DOCX)

Appendix S2 Supplemental scatter plots and linear regression lines for the analysis of interobserver agreement.
(DOCX)

Appendix S3 Extended results regarding the ANOVA analysis and post-hoc tests of differences in anatomic parameters of patients who underwent implantation of the large, middle or small version of either valve.
(DOCX)

Appendix S4 Extended results regarding the analysis of differences in predictive values of the various anatomic

parameters for the valve size considered optimal by the TAVI team.
(DOCX)

Author Contributions

Conceived and designed the experiments: FS PL DZ MG PB CS MFR CK HCB. Performed the experiments: FS PL DZ MG. Analyzed the data: FS PL DZ MG CK HCB. Contributed reagents/materials/analysis tools: MFR HCB. Wrote the paper: FS PL DZ MG PB CS MFR CK HCB.

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2.2. Semi-automatic CT-angiography based evaluation of the aortic annulus in patients prior to TAVR: interchangeability with manual measurements.

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ORGINAL PAPER

Semi-automatic CT-angiography based evaluation of the aortic annulus in patients prior to TAVR: interchangeability with manual measurements

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Abstract
To compare a semi-automatic software tool for the measurement of aortic annulus dimensions with manual measurements by expert readers and to analyze whether and to what extent interchangeability exists between semi-automatic and manual measurements. We retrospectively included 374 consecutive patients with high-grade aortic stenosis who had undergone CT-angiography of the heart prior to trans-catheter aortic valve replacement (TAVR). In independent analyses, two expert readers manually measured aortic annulus dimensions (long axis, short axis, circumference, area) as well as the distance of the coronary ostia from the annulus plane. A third independent reader performed annulus evaluation using a software tool for semi-automatic detection and measurement of the annulus plane. Intraclass correlation coefficients (ICC) and Bland–Altman analysis was used to compare both manual measurements as well as manual and semi-automatic measurements of annulus parameters. Using the respective measurements we simulated size selection for a Sapien XT transcatheter heart valve (THV). Interchangeability of methods was addressed by calculation of the estimated individual equivalence index γ. There was excellent agreement between both expert observers in manual measurements of the annulus with ICC's in the range 0.89–0.94 for all anatomic parameters. Similar high agreements were observed between semi-automatic and manual measurements, with ICC's in the range of 0.89–0.95. THV size recommendation based on manual versus semiautomatic measurements agreed in 80.7% of cases while agreement between both expert readers concerning THV size recommendation was 80.6%. Semi-automatic measurements of anatomic parameters of the aortic root show high agreement and interchangeability with manual measurements in CT-angiography prior to TAVR.

Keywords Trans-catheter aortic valve replacement · Trans-catheter aortic valve implantation · TAVR · TAVI · Aortic annulus · Valve sizing · Annulus sizing

Introduction

In the Western world, aortic valve stenosis is the most common acquired valve disorder and severe forms have detrimental outcomes, especially when treated by medication only [1]. Over the last decade, trans-catheter aortic valve replacement (TAVR)—developed for patients too sick to undergo open heart surgery or with high perioperative risk [2–4]—has emerged as a novel, less invasive treatment alternative. With over 100,000 trans-catheter aortic heart valves (THV) implanted worldwide since the initial description in 2002, this technique has been quickly adopted both by the cardiological and cardiac-surgery community [5]. In recent randomized trials its application has been extended to patients with intermediate perioperative risk [6].

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Unlike in open heart surgery, during TAVR the interventionalist does not have direct access to the aortic annulus and has to rely on imaging to assess its dimensions. With its complex geometric shape, imaging modalities providing a three-dimensional evaluation of the aortic valve are generally preferred over two-dimensional modalities, such as standard echocardiography. In particular, CT angiography has become the gold standard in this arena due to its wide availability, high spatial resolution and panoramic visualization of the aortic valve as well as the simultaneous visualization of the catheter access route [7].

By careful assessment of aortic root geometry, the radiologist plays an integral role in patient selection and treatment planning for TAVR. Size and configuration of the aortic annulus, the degree of calcification and distance of the coronary ostia from the annulus plane are of paramount importance for the optimal selection of prosthesis model and size. Some studies have suggested that valve size selection based on MDCT improves outcomes with higher procedural success rates and fewer patients developing post-interventional aortic regurgitation [8].

Recently, software tools have become available which provide automatic or semiautomatic measurements of aortic root parameters [9–13]. Based on well-defined algorithms, these tools promise to provide highly reproducible annulus measurements thus considerably reducing interobserver variability.

In this study, we analyze the reproducibility of manual measurements of the aortic annulus parameters between two experienced observers and compare these results with annulus parameters obtained by a semi-automatic software tool in a large cohort of patients with severe aortic valve stenosis. We address the influence that perceived image quality, signal-to-noise ratio and the extent of calcification of the aortic valve has on the reproducibility of these measurements. Finally, we analyze to what extent differences in measurements would translate into changes of recommended valve size and address the interchangeability of the semiautomatic with the manual measurements.

Materials and methods

Patient population

Our analysis included consecutive patients with severe aortic valve stenosis confirmed by echocardiography who were referred for CT angiography for the evaluation of aortic root anatomy between November 2007 and June 2012. According to our institutional policies, patients with impaired renal function (estimated glomerular filtration rate < 30 ml/min), suppressed TSH-levels or a history of allergic reaction to iodine-containing contrast agents were excluded. After explicit information about the risks of iodine-containing contrast agents and exposure to X-rays, written informed consent was obtained. This consent included an anonymous analysis of the image data acquired.

Since all diagnostic CT scans were performed during routine clinical workup prior to potential TAVR and were analyzed only after anonymization, the institutional review board of our institution waived the necessity to obtain informed consent beyond routine clinical requirements.

CT data acquisition and image reconstruction

CT scans were performed on a first-generation dual-source MDCT scanner (n = 52, Somatom Definition, Siemens Healthineers, Erlangen, Germany) or on a second-generation dual-source MDCT scanner (n = 322, Somatom Flash, Siemens Healthineers) as described elsewhere [14].

The ECG-signal was registered continuously throughout all scans. Slice collimation was $2 \times 64 \times 0.6$ mm (first generation scanner) or $2 \times 128 \times 0.6$ mm (second generation scanner). In patients scanned on the first generation scanner a prospectively ECG-triggered acquisition protocol with image acquisition during diastole (65% of RR interval) was chosen with the scanrange centered on the heart. Gantry rotation time was 330 ms. Tube potential was selected depending on patient weight (100 kV if weight ≤ 85 kg, otherwise 120 kV). Effective tube current–time product was 400 mA s.

On the second generation scanner, a high-pitch protocol was applied (pitch factor = 3.2). Tube potential was adjusted to patient weight, either manually (n = 191, 100 kV if weight ≤ 85 kg, otherwise 120 kV) or automatically on the basis of the topogram (n = 131, Care-kV, Siemens Healthineers). Gantry rotation time was 280 ms. An online tube current modulation software was used for all scans (Care Dose 4D, Siemens Healthineers) with a reference tube current–time product set to 350 mA s per rotation. A craniocaudal scan direction was chosen, with image acquisition of the heart beginning at 60% of the RR interval. Scan range included the heart only (first generation scanner) or the entire body trunk to the level of the inguinal region (second generation scanner).

In all patients, 90 ml of iomeprol 816.5 g/l (Imeron 400, Bracco Imaging, Milan, Italy) were administered via an ante-cubital vein at a flow rate of 4 ml/s, followed by 100 ml of normal saline at the same flow rate. Contrast enhancement was detected by bolus tracking within the ascending aorta.

Once intraluminal attenuation exceeded 150 HU, the table was repositioned automatically to cover the desired scan range. Delay was 6 s (first generation) or 12 s (second

generation). Thereafter, the start of the scan was triggered by ECG automatically.

Standard coronary CTA reconstructions were obtained using a medium-smooth convolution kernel (B26f, small field of view, slice thickness 0.75 mm, reconstruction increment 0.5 mm covering the entire heart). All series were anonymized and transferred to an external workstation for further analysis.

CT data analysis

Two expert readers (radiologists with 12 and 10 years' experience in cardiovascular CT) used commercially available software (Syngo Via VA20, Siemens Healthineers) to independently analyze all datasets. Readers assessed subjective image quality on a 5-point Likert scale and the degree of valve calcifications on a 3-point Likert scale. Patients were excluded from further analysis if at least one reader attributed the lowest image quality score to a dataset (n = 9). One of the expert readers estimated SNR in the ascending aorta by measuring average attenuation and standard deviation within a circular region of interest (ROI) with a diameter of approx. 1 cm within the ascending aorta.

Furthermore, both readers determined aortic annulus size according to the techniques most widely applied: Using multiplanar reformations ('Basic 3D' Workflow in Syngo Via VA20, Siemens Healthineers), readers established the aortic annulus plane defined by the three 'hinge' points (i.e. the most apical attachment points of the valvular cusps). Both readers then manually determined the length of the long axis, short axis, circumference and area of the aortic valve annulus. Furthermore, the distance of the coronary ostia from the annulus plane was measured (Fig. 1). Both readers performed this analysis independently for each patient.

A third reader (radiologist with 3 years' experience both in manual and semi-automatic evaluation of the aortic annulus) then performed annulus evaluation using a commercially available software tool for the automatic detection and measurement of the aortic annulus plane ('Valve Pilot' within the 'CT Cardiac Function' workflow of SyngoVia VA20, Siemens Healthineers). The software was used to semi-automatically determine diameters of long axis, short axis, area and circumference-derived effective annulus diameter (d_{eff_C}) as well as the distance of the coronary ostia from the annulus plane. For comparison with manual measurements Circumference-derived effective annulus diameter was transformed into circumference (C) according to the formula

$$C = d_{eff\_C} \times \pi.$$

The automatically detected annulus plane and annulus contour could be manually changed if deemed necessary (Figs. 2, 3). The third reader was blinded towards all manual measurements.

Optimal THV size and quantification of discordance in measurements

The parameter 'annulus area' was used to determine optimal THV size of a hypothetical Sapien XT THV based on an algorithm suggested by Binder et al. [8] implementing a slight valve oversizing. Optimal THV size was derived from both manual measurements, from the average of both manual measurements as well as from semi-automatic measurements. The 20-mm THV was recommended if the area was < 3.15 cm^2, the 23-mm-THV was recommended if the area was in the range of at least 3.15 to < 4.15 cm^2, the 26-mm-THV was recommended for areas in the range of at least 4.15 to < 5.3 cm^2 and the 29-mm-THV was recommended for areas of at least 5.3 cm^2.

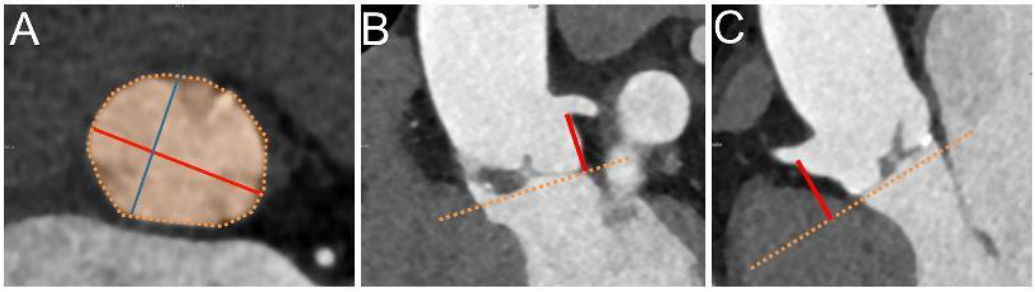

Fig. 1 Anatomic parameters of the aortic annulus under consideration: **a** aortic annulus plane with long axis (red), short axis (blue), circumference (orange dotted line) and area (translucent orange area); **b** orthogonal view of the left coronary cusp demonstrating distance of the left ostium from the annulus plane (red line); **c** orthogonal view of the right coronary cusp demonstrating distance of the right coronary ostium from the annulus plane (red line)

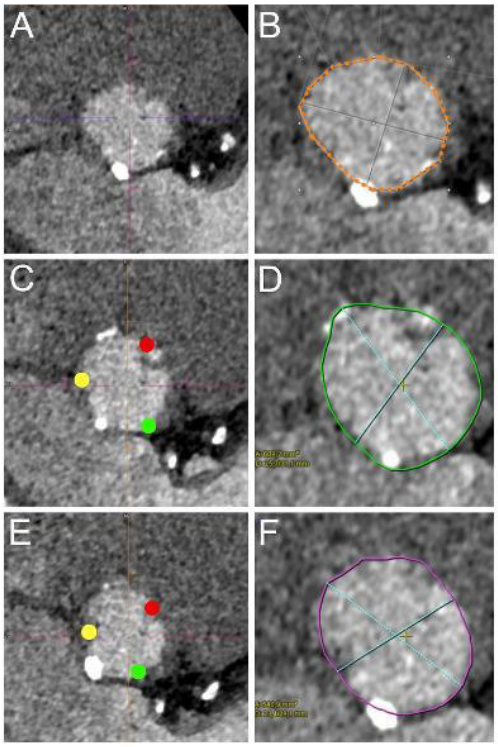

Fig. 2 Manual (**a, b**) and semi-automatic (**c, f**) annulus measurement applying a two-step correction process: **a, b** demonstrate the goldstandard, the plane (**a**) and contour (**b**) established by reader 1 manually. **c, d** Demonstrate the annulus plane and contour initially proposed by the software. This plane was slightly corrected to meet the definition of the annulus plane based on the three 'hinge' points (**e**) followed by an adjustment of the annulus contour (**f**), resulting in images that highly resemble the manually established measurements

If the suggested THV size differed between readers for the manual measurements or between manual and semi-automatic measurements, the degree of discordance of the underlying parameter (annulus area) was quantified on a 3-point scale: 'mild' for differences < 5%, 'moderate' for differences in the range 5–10% and 'severe' for differences of at least 10%. Furthermore, in the subgroup of patients with 'severe' differences, the median and interquartile ranges of differences were calculated.

Statistical analysis

Continuous variables are reported as mean ± standard deviation when normally distributed, otherwise as median (interquartile range). The D'Agostino–Pearson test was used to test for normal distribution of continuous variables.

To quantify agreement between observers as well as between semi-automatic and manual measurements, Cohen's kappa was used in the case of categorical variables and was reported with 95% confidence interval. For continuous variables, the intraclass correlation coefficient (ICC) was used and reported with 95% confidence interval. Bland–Altman plots were used to address any bias between observations and to quantify the extent of random fluctuations of each method.

Furthermore, interchangeability of semi-automatic annulus measurements with manual measurements regarding the derived recommendation of valve size was determined using a method proposed by Obuchowski et al. [15, 16] evaluating interchangeability in the absence of a reference standard by using the estimated individual equivalence index γ in a different-reader scenario.

Differences in proportions were assessed using the Chi squared test.

p values of 0.05 or less were considered statistically significant. Data were analyzed using MedCalc Statistical

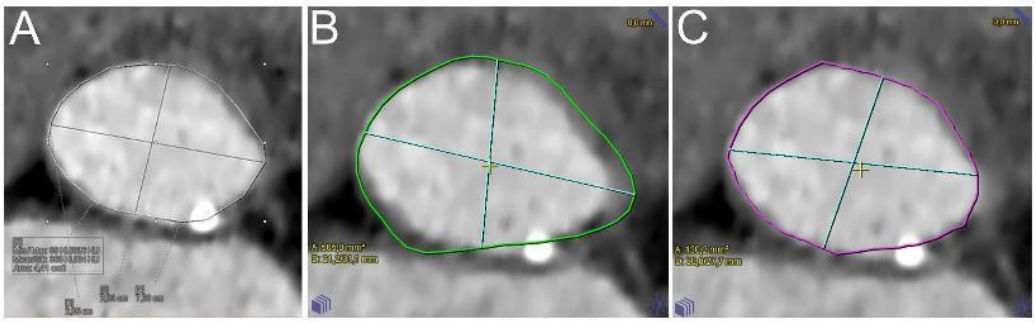

Fig. 3 Manual (**a**) and semi-automatic annulus measurement in a patient applying a one-step correction process: automatic annulus detection was considered good (**b**) and only aortic annulus contour had to be adjusted slightly (**c**)

Software version 13.0 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014) and SPSS (21.0, IBM, Armonk, USA).

Results

Patient population

Between November 2007 and June 2012, a total of 374 patients were referred to our department for a CT-angiography of the thorax and abdomen for TAVR evaluation and underwent TAVR at the department of cardiology within 3 months after the scan. In all patients, severe aortic valve stenosis (i.e. AVA < 1.0 cm^2) had been confirmed by echocardiography prior to referral to our department. 19 patients were excluded from this analysis (in nine patients, a high-pitch scan protocol without ECG-synchronization had been performed, nine patients were excluded due to insufficient image quality and one patient due to a large subvalvular aneurysm which impeded software-based annulus detection). Table 1 lists baseline characteristics of the 355 patients in the evaluated study population.

Table 1 Patients baseline characteristics (N = 355), N (%), mean ± SD or median (interquartile range)

Age (years)	82 (77; 86)
Male	156 (43.9%)
BSA	1.79 (1.66; 1.93)
BMI	25.4 (23.0; 29.4)
Diabetes	96 (27.0%)
Hyperlipidemia	153 (43.1%)
Hypertension	286 (80.6%)
Current smoker	48 (13.5%)
Previous pacemaker	41 (11.5%)
Previous atrial fibrillation	108 (30.4%)
CAD	192 (54.1%)
1-vessel CAD	43 (12.1%)
2-vessel CAD	48 (13.5%)
3-vessel CAD	101 (28.5%)
Previous CABG	39 (11.0%)
Known peripheral artery disease	32 (9.0%)
Cerebrovascular disease	36 (10.1%)
COPD	48 (13.5%)
eGFR (ml/min/1.73 m^2)	55.1 ± 19.1
Logistic EuroSCORE	18.9 (13.3; 25.7)
Aortic valve area (cm^2)	0.70 (0.60; 0.80)
Maximum pressure gradient (mmHg)	65 (50; 80)
LVEF (%)	60 (47; 67.3)
Aortic regurge (more than mild)	59 (16.6%)
Mitral regurge (more than mild)	89 (25.1%)

Assessment of image quality, valve calcification and signal-to-noise ratio (SNR)

There was good agreement between both readers for the semiquantitative assessment of overall image quality at the aortic annulus ($\kappa = 0.78 \pm 0.02$) as well as the amount of calcification ($\kappa = 0.62 \pm 0.03$). Therefore, image quality ratings and calcification ratings of reader 1 were used for further analysis. Estimated SNR within the ascending aorta was 12.2 (9.04; 15.71).

Interobserver variability for manual measurements of the aortic root and agreement in prosthesis size selection

There was excellent correlation between both observers in manual measurements of aortic root parameters with ICC's consistently close to or above 0.90 for all annulus parameters. Across all patients, observer agreement was slightly but significantly higher for annulus area and circumference than for diameters of long and short axis (ICC's: 0.94 and 0.93 vs. 0.89 and 0.89, $p < 0.001$, Table 2; Fig. 4).

There was no significant difference in observer agreement between the subgroup with excellent or good image quality (IQ 4 or 5; n = 258) and the subgroup with lower image quality ratings (IQ 2 or 3; n = 97) except for the distance of the right coronary ostium, in which agreement was slightly but significantly higher in the subgroup with high image quality (ICC = 0.78 vs. 0.65; $p = 0.025$, "Appendix 1").

Applying the algorithm proposed by Binder et al. for the selection of a Sapien XT valve, both readers agreed in THV size in 81% (287/355) of patients. In the remaining 68 patients, readers recommended different THV sizes. In

Table 2 Interobserver agreement for manual measurements of the aortic root reported as intraclass correlation coefficient and Bland–Altman-analysis parameters

	Diameter long axis	Diameter short axis	Annulus circumference	Annulus area	Distance of left coronary ostium	Distance of right coronary ostium
ICC (95% CI)	0.89 (0.87; 0.91)	0.89 (0.86; 0.91)	0.93 (0.92; 0.95)	0.94 (0.93; 0.96)	0.78 (0.74; 0.82)	0.75 (0.70; 0.79)
Mean difference	0.00 cm	0.01 cm	0.07 cm	0.04 cm^2	0.01 cm	0.05 cm
SD of differences	0.12 cm	0.11 cm	0.24 cm	0.27 cm^2	0.19 cm	0.24 cm

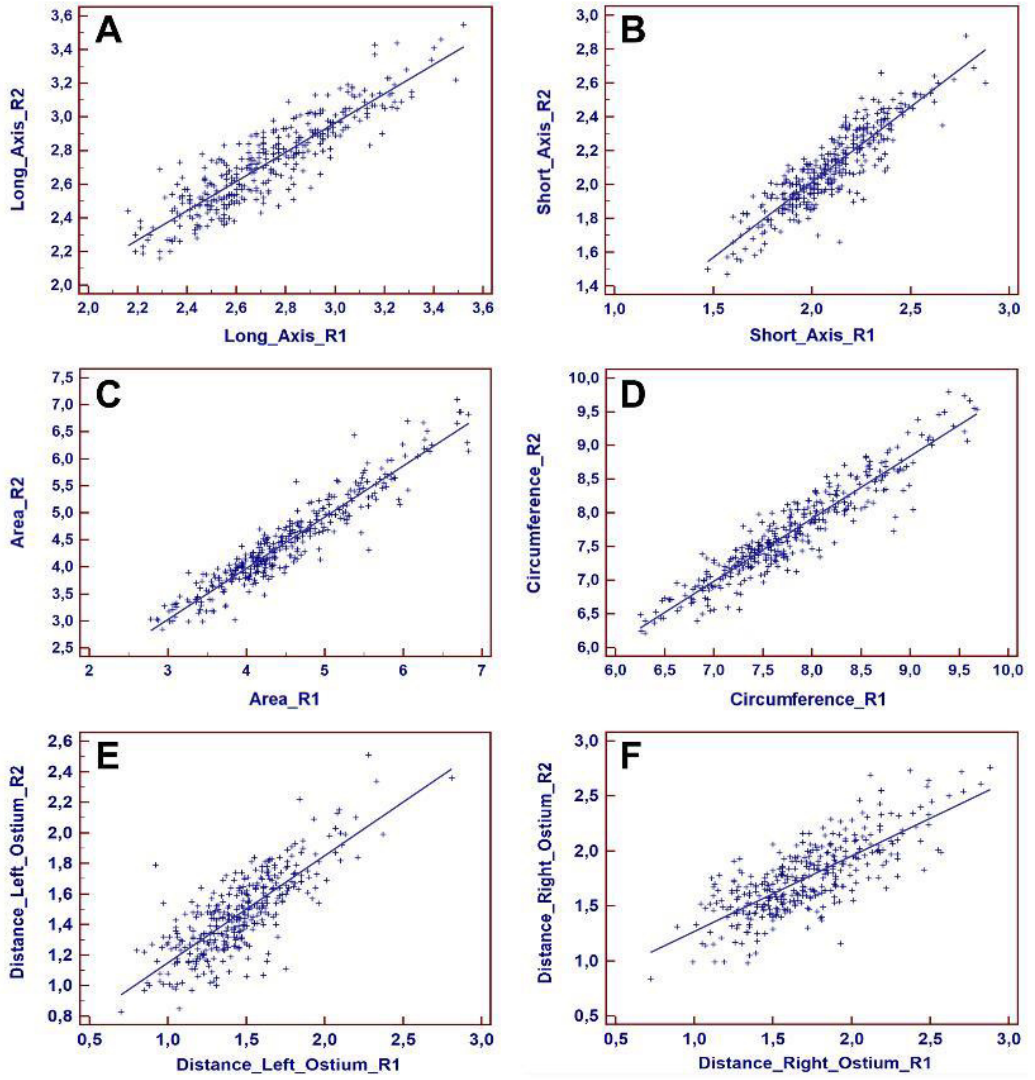

Fig. 4 Scatter plots and regression lines demonstrating the correlation of manual measurements of aortic annulus parameters between both readers: **a** long axis, **b** short axis, **c** area, **d** circumference, **e** distance of the left ostium, **f** distance of the right ostium

these patients, the underlying discordance in annulus area was mild (< 5%) in 35% (24/68) of patients, moderate (5% to < 10%) in 44% (30/68) and severe (at least 10%) in 21% (14/68) of patients. Median difference in patients with severe discordance was 11.7% (11.2%; 13.5%).

Performance of semi-automatic measurements and agreement with manual measurements

Because of excellent interobserver agreement in manual measurements, the mean of both observers was used for comparison with automatic measurements.

For semi-automatic measurements, the automatically detected annulus plane had to be adjusted in 11% (38/355) of cases. Adjustments of the annulus contour without changes in the automatically suggested plane were necessary in 79% (282/355) of cases. No user-interaction with the suggested annulus segmentation was required in 10% of cases (35/355).

Across all patients, there was excellent agreement between semi-automatic and manual measurements with ICC's close to or above 0.90. Agreement in measurements of annulus area and circumference were slightly but significantly higher than for measurements of long axis and short axis diameter (0.95 and 0.95 vs. 0.89 and 0.86, n = 355, p < 0.01, Table 3; Fig. 5).

Agreement of semi-automatic measurements in subgroups according to image quality, SNR and annulus calcifications

Differences in agreement between the subgroups with excellent and good image quality (IQ 4 or 5; n = 258) and the subgroup with lower image quality ratings (IQ 2 or 3; n = 97) were not statistically significant (Table 3).

Accordingly, differences in agreement between patients with $SNR > SNR_{median}$ and patients with $SNR < SNR_{25th\ percentile}$ were not statistically significant. Furthermore, there were no significant differences in agreement of the various parameters between patients with mild, moderate or severe calcifications of the aortic valve ("Appendix 2").

Comparison of prosthesis size selection based on manual versus automatic measurements

Using the algorithm proposed by Binder et al. semi-automatic measurements resulted in identical THV size selection in 82% (290/355) of patients. In the remaining 18% (65/355) of patients, semi-automatic measurements would have resulted in a different THV size recommendation. In these patients, the underlying discordance in annulus area was mild (< 5%) in 40.0% (26/65) of patients, moderate (5 to < 10%) in 38.5% (25/65) and severe (at least 10%) in 21.5% (14/65) of patients. Median difference in patients with severe discordance was 15.8% (13.2%; 16.6%).

Importantly, the frequency of these differences in size recommendations were not significantly different from those observed by using independent measurements from two experienced observers (18.3%; 65/355 vs. 19.2%; 68/355, p = 0.85).

Using the method proposed by Obuchowski et al. [15], the valve size recommendation on the basis of expert readers' manual determination of valve size agreed with the recommendation on the basis of the semiautomatic method in 80.7% (573/710) of cases (γ). On the other hand, the probability of agreement in valve size recommendation based on the two manual measurements by expert readers was nearly identical with 80.6% (286/355).

Discussion

In this study, we analyze the performance of a software tool for the semi-automatic measurement of anatomic parameters of the aortic root in a large cohort of patients with

Table 3 Agreement between manual and automatic measurements of the aortic root reported as intraclass correlation coefficient and Bland–Altman-analysis parameters

	Diameter long axis	Diameter short axis	Annulus circumference	Annulus area	Distance of left coronary ostium	Distance of right coronary ostium
All patients (n = 355)						
ICC (95% CI)	0.89 (0.87; 0.91)	0.86 (0.83; 0.88)	0.95 (0.93; 0.96)	0.95 (0.94; 0.96)	0.70 (0.64; 0.75)	0.75 (0.70; 0.79)
Mean difference	0.02 cm	0.02 cm	0.01 cm	0.07 cm^2	0.00 cm	0.04 cm
SD of differences	0.12 cm	0.13 cm	0.23 cm	0.27 cm^2	0.23 cm	0.25 cm
Sub-group IQ 4 or 5 (n = 258)						
ICC (95% CI)	0.87 (0.87; 0.92)	0.85 (0.81; 0.88)	0.94 (0.93; 0.95)	0.95 (0.93; 0.96)	0.72 (0.66; 0.77)	0.76 (0.71; 0.81)
Mean difference	0.02 cm	0.01 cm	0.01 cm	0.08 cm	0.01 cm	0.04 cm
SD of differences	0.11 cm	0.12 cm	0.23 cm	0.26 cm	0.22 cm	0.25 cm
Sub-group IQ 2 or 3 (n = 97)						
ICC (95% CI)	0.88 (0.83; 0.92)	0.89 (0.83; 0.92)	0.95 (0.93; 0.97)	0.95 (0.93; 0.97)	0.63 (0.51; 0.73)	0.69 (0.58; 0.78)
Mean difference	0.02 cm	0.02 cm	0.01 cm	0.05 cm^2	0.00 cm	0.03 cm
SD of differences	0.14 cm	0.13 cm	0.24 cm	0.29 cm^2	0.26 cm	0.25 cm
p for difference in ICC's	0.72	0.17	0.43	1.0	0.17	0.22

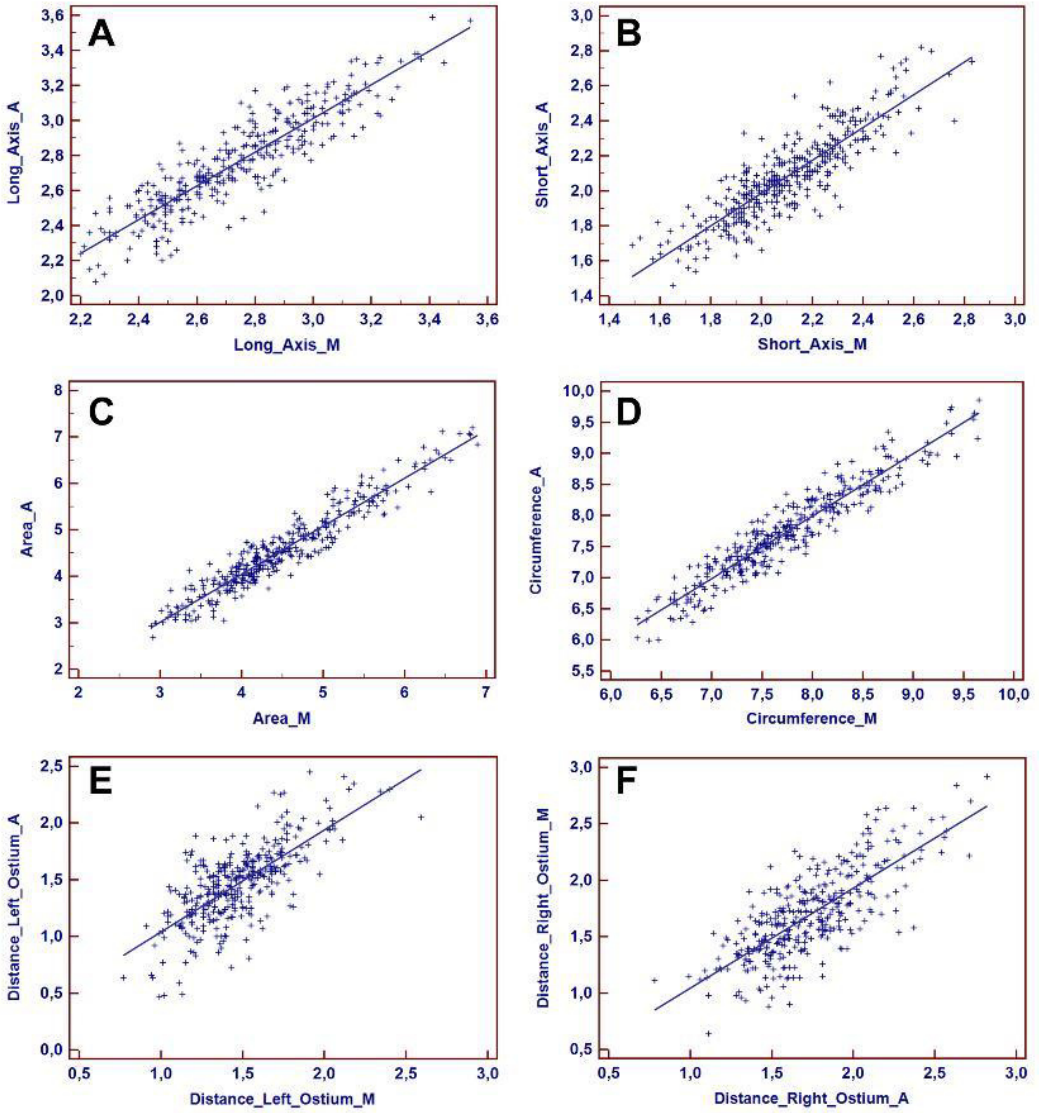

Fig. 5 Scatter plots and regression lines demonstrating correlation of manual and semi-automatic measurements of aortic annulus parameters: **a** long axis, **b** short axis, **c** area, **d** circumference, **e** distance of the left ostium, **f** distance of the right ostium

high-grade aortic stenosis. We first address reproducibility of manual annulus measurements and show that there is excellent agreement between two experienced readers regardless of perceived image quality, with highest agreements found for annulus circumference and area. When selecting THV size on the basis of annulus area according to an algorithm proposed by Binder et al. [8] and applying fixed thresholds, readers suggested the same THV size in 81% (287/355) of patients.

Secondly, we demonstrate excellent agreement of the semi-automatic measurements with the mean values of both observers used as reference standard. This was observed

regardless of perceived image quality, SNR or the degree of valve calcifications. Applying the THV size selection algorithm accordingly, manual versus semi-automatic measurements would have resulted in the same THV size suggestion in 82% (290/355) of patients, thus confirming the high similarity of the semi-automatic measurements to a different set of manual measurements from an experienced observer.

We conclusively demonstrate that semiautomatic measurements are interchangeable with measurements performed by expert readers in the sense proposed by Obuchowski et al. [15].

At first glance, the frequency of discrepancies in THV size recommendations (in around 19% of cases) appears high both for repeated manual measurements as well as semi-automatic analysis; however, it has to be taken into account that a significant proportion of patients will be suitable candidates for two THV sizes. These discrepancies in THV recommendations would be greatly attenuated by applying a THV selection algorithm that accounts for such "grey zones"; since our intention was to analyze whether semi-automatic analysis yields interchangeable measurements, we do not consider the rigid three-threshold algorithm a limitation of our study.

As expected in patients with high-grade aortic valve stenosis, 73% (258/355) of patients had at least moderate valve calcifications, potentially compromising automatic detection. Nevertheless, we found semi-automatic detection to be feasible in all but one patient, who had a large subvalvular outflow tract aneurysm. Similar to the results by Foldyna et al. [11] and somewhat paradoxically, automatic annulus plane detection was successful in the vast majority of cases (89%, 317/355), whereas exact contour detection within the correct plane proved more difficult for the software algorithm: contour adjustments had to be performed in 89% (282/317) of cases in which the plane was detected correctly.

Taken together, our results demonstrate that semi-automatic measurements of anatomic parameters of the aortic root have high agreement with manual measurements by expert readers and are truly interchangeable.

Our results are in line with but also extend those of Foldyna et al. [11] and Lou et al. [17] who used the same semiautomatic software tool evaluated in our study: we also report excellent agreement between semi-automatic and manual measurements; due to the significantly higher number of patients (355 vs. 30 and 110, respectively), however, we provide analyses for various image quality subgroups as well as for different degrees of aortic valve calcification and demonstrate that within the commonly observed ranges there is no measurable impact on the degree of agreement.

Our study has several limitations. First, we compare semi-automatic measurements with manual evaluations of the same datasets and cannot provide an independent gold standard for annulus size (such as direct measurements during surgery). Therefore, our study cannot address true test accuracy of the semi-automatic measurements. However, our reference standard is derived from independent manual measurements by two experienced readers and is thus optimally suited to define the values that the software tool under evaluation is supposed to generate. Furthermore, the method of addressing interchangeability conceptually circumvents an objective goldstandard.

Second, we did not quantify the time required for manual versus semi-automatic measurements. Therefore, our study does not address or quantify the reduction in evaluation time achieved with the use of a semi-automatic software tool. Such significant reductions are well documented in a study by Foldyna et al. [11] both for experienced and inexperienced observers using the same software tool as in our study.

The measurement of the evaluation time frequently proves difficult to perform in an objective and accurate way and carries the risk of influencing measurements when readers feel time constraints. On the contrary, we encouraged readers to apply greatest care for annulus plane definition and annulus contour delineation and to report values only after reaching highest possible levels of diagnostic confidence.

Third, due to the scan protocols implemented at our institution at the time, all datasets were acquired in diastole. Therefore, our findings would have to be reproduced with systolic datasets to confirm a high agreement between manual and semi-automatic measurements regardless of cardiac phase.

Despite these limitations, our results confirm the clinical value of semi-automatic aortic annulus detection, while also highlighting the importance of an experienced reader for the validation and adjustment of automatically generated measurements at this stage of software evolution. Considering the various recent clinical implementations of deep learning algorithms significant advances in this field are to be expected.

Compliance with ethical standards

Conflict of interest Konstantin Nikolaou, Fabian Bamberg and Florian Schwarz have received speaker honoraria from Siemens Healthineers. Konstantin Nikolaou has received speaker honoraria from Bracco Imaging Deutschland GmbH. Fabian Bamberg has received an unrestricted research grant from Bayer Healthcare AG. All other authors declare that they have no conflicts of interest.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. This article does not contain any studies with animals performed by any of the authors.

Informed consent All patients gave informed consent for MDCT. Due to the retrospective nature of this study, the local IRB waived the necessity to obtain informed consent beyond these routine clinical requirements.

Appendix 1

Agreement between manual measurements of the aortic root by reader 1 and reader 2 reported as intraclass correlation coefficient and Bland–Altman-analysis parameters in image quality subgroups.

	Diameter long axis	Diameter short axis	Annulus circumference	Annulus area	Distance of left coronary ostium	Distance of right coronary ostium
Sub-group IQ 4 or 5 (n = 258)						
ICC (95% CI)	0.90 (0.87; 0.92)	0.89 (0.86; 0.91)	0.94 (0.92; 0.95)	0.94 (0.93; 0.96)	0.79 (0.74; 0.83)	0.78 (0.72; 0.82)
Mean difference	0.00 cm	0.01 cm	0.05 cm	0.03 cm^2	0.02 cm	0.06 cm
SD of differences	0.12 cm	0.11 cm	0.23 cm	0.26 cm^2	0.18 cm	0.24 cm
Sub-group IQ 2 or 3 (n = 97)						
ICC (95% CI)	0.88 (0.83; 0.92)	0.89 (0.84; 0.93)	0.93 (0.90; 0.95)	0.95 (0.92; 0.96)	0.74 (0.64; 0.82)	0.65 (0.52; 0.75)
Mean difference	0.00 cm	0.00 cm	0.11 cm	0.07 cm^2	0.01 cm	0.04 cm
SD of differences	0.14 cm	0.12 cm	0.26 cm	0.29 cm^2	0.19 cm	0.25 cm
p for difference in ICC's	0.42	1.0	0.51	0.44	0.32	0.03

Appendix 2

Agreement between manual and semiautomatic measurements in various subgroups:

Signal-to-noise ratio (SNR)

	Diameter long axis	Diameter short axis	Annulus circumference	Annulus area	Distance of left coronary ostium	Distance of right coronary ostium
$SNR > SNR_{median}$ (n = 167)						
ICC (95% CI)	0.89 (0.86; 0.92)	0.86 (0.81; 0.89)	0.95 (0.93; 0.96)	0.95 (0.94; 0.96)	0.69 (0.62; 0.76)	0.75 (0.68; 0.81)
Mean difference	0.03 cm	0.01 cm	0.01 cm	0.08 cm^2	0.01 cm	0.04 cm
SD of differences	0.13 cm	0.13 cm	0.22 cm	0.26 cm^2	0.23 cm	0.26 cm
$SNR < SNR_{25th\ percentile}$ (n = 87)						
ICC (95% CI)	0.88 (0.82; 0.92)	0.88 (0.82; 0.92)	0.92 (0.88; 0.95)	0.93 (0.90; 0.95)	0.75 (0.64; 0.83)	0.74 (0.64; 0.82)
Mean difference	0.01 cm	0.03 cm	0.02 cm	0.04 cm^2	0.03 cm	0.03 cm
SD of differences	0.12 cm	0.12 cm	0.29 cm	0.31 cm	0.23 cm	0.26 cm
p value for difference of ICC's	0.73	0.54	0.07	0.20	0.35	0.87

Degree of calcification

	Diameter long axis	Diameter short axis	Annulus circumference	Annulus area	Distance of left coronary ostium	Distance of right coronary ostium
Calcifications = 1 (n = 97)						
ICC (95% CI)	0.88 (0.82; 0.92)	0.86 (0.80; 0.90)	0.92 (0.89; 0.95)	0.93 (0.90; 0.95)	0.63 (0.49; 0.73)	0.79 (0.71; 0.85)
Mean difference	0.02 cm	0.02 cm	0.01 cm	0.10 cm	0.00 cm	0.06 cm
SD of differences	0.12 cm	0.12 cm	0.25 cm	0.27 cm	0.24 cm	0.24 cm

	Diameter long axis	Diameter short axis	Annulus circumference	Annulus area	Distance of left coronary ostium	Distance of right coronary ostium
Calcifications = 2 (n = 205)						
ICC (95% CI)	0.89 (0.86; 0.92)	0.86 (0.82; 0.89)	0.95 (0.94; 0.96)	0.95 (0.94; 0.96)	0.71 (0.64; 0.76)	0.71 (0.63; 0.77)
Mean difference	0.02 cm	0.05 cm	0.01 cm	0.05 cm	0.00 cm	0.04 cm
SD of differences	0.13 cm	0.27 cm	0.22 cm	0.27 cm	0.23 cm	0.26 cm
Calcifications = 3 (n = 53)						
ICC (95% CI)	0.90 (0.84; 0.94)	0.85 (0.76; 0.91)	0.94 (0.90; 0.97)	0.95 (0.92; 0.97)	0.76 (0.61; 0.85)	0.81 (0.69; 0.88)
Mean difference	0.03 cm	0.03 cm	0.02 cm	0.08 cm^2	0.04 cm	0.02 cm
SD of differences	0.12 cm	0.11 cm	0.24 cm	0.26 cm^2	0.22 cm	0.23 cm

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4. Veröffentlichungen

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