# The Traditional Intramedullary Axis Underestimates the Medial Tibial Slope Compared to Transmalleolar Sagittal Axis in Image-based Robotic-Assisted Unicompartimental Knee Arthroplasty

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Isolated medial compartment osteoarthritis (OA) has been reported to be present in  $85\%$ <sup>1</sup> of the knees presenting with clinical OA and it remains a challenging problem due to its economic and healthcare management implications. Surgical management of unicompartmental knee arthritis includes joint-preserving treatment such as arthroscopic debridement or high tibial osteotomy (HTO) and no-joint preserving treatment such as unicompartmental arthroplasty or total knee arthroplasty  $(TKA)^2$  These procedures have a finite life span

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in young and active patients, and concerns like functional recovery and the ability to return to sports activities should be considered. In recent years, the use of HTO for the treatment of end-stage medial knee osteoarthritis has decreased.<sup>3</sup> It has been demonstrated that HTO remains an attractive joint-preserving procedure to avoid a knee arthroplasty for patients younger than 50 years with low-grade unicompartmental OAand a varus knee who have an extraarticular deformity of the tibia.<sup>4</sup> However, the HTO risk of failure increased

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dramatically for patients with OA who were rated as Ahlback grade 2 or higher.<sup>4</sup> In the last decade, medial unicompartmental knee arthroplasty (UKA) has been recognized as an excellent treatment option for end-stage medial knee  $OA<sup>5</sup>$  and has been increasingly used in clinical practice.<sup>6</sup> It has the advantage of minimal invasiveness, fast recovery, less bleeding, conservation of functional knee structures, less soft tissue injury, and bonestock conservation.<sup>7,8</sup> Knee function and patient satisfaction are superior to total knee arthroplasty.<sup>9,10</sup> Recent studies have shown that in patients aged 60 years or younger, UKA survival rates are 90% at 10 years.<sup>11</sup> Patients who underwent UKA had better articular excursion, and were more satisfied and more active, according to a functional assessment based on the Bristol score.<sup>7</sup> The failure of UKA is associated with multiple factors such as prosthesis design, surgeon experience, patient selection, polyethylene (PE) quality, and intraoperative alignment and fixation. In particular, the correct alignment and implant position are paramount for the long-term survival of UKA since those can alter the biomechanics of the knee, increasing ligament strain and contact stresses.<sup>12</sup>

Typical indications for UKA are a stable knee, functionally intact lateral and femoropatellar compartments, correctable (intra-articular) varus deformity, less than 10 to15 degreesof fixed flexion deformity, and flexion beyond 100degrees. Outside these indications, typically a patient should be addressed to a total knee arthroplasty. The anterior cruciate ligament (ACL) insufficiency, is reported as a relative contraindication for UKA implantation, leading to high failure rates,<sup>12</sup> however, many authors in the recent literature reported no increased revision rate compared to conventional UKA.<sup>13,14</sup> The ACL forces after UKA are comparable to those in native knees, indicating a similar role of the ACL in knees following UKA.<sup>15</sup> Suggs et al demonstrated in cadaveric knees that Antero-Posterior stability of the knee after UKA with an intact ACL was similar to that of the native knee, while UKA with a deficient ACL showed more than twice the knee movement under anterior tibial loading.<sup>16</sup> The posterior tibial slope (PTS) of the medial tibial plateau (MTP) is considered an important anatomical factor that affects both the ACL function and sagittal plane stability of the knee.<sup>17</sup> The PTS is defined as the posterior inclination of the plateau relative to the tibial bone  $axis.<sup>18</sup>$ 

As originally described by the Knee Society Total Knee Arthroplasty Roentgenographic Evaluation and Scoring System, the PTS is measured radiographically with a best-fit line along the tibial canal to the tibial baseplate on the sagittal plane radiograph. However, in most computer-navigated or robotic medial unicompartmental knee arthroplasties (mUKAs), reference points are taken from the malleoli, and the PTS is set from a transmalleolar axis (TMA) rather than an intramedullary axis (IMA) as it is traditionally measured radiographically.<sup>16</sup> There areno data, to our knowledge, on the implications of the different methods in setting PTS for mUKA. Therefore, this study aimed to assess the differences between the TMA and the IMA of patients with knee arthritis undergoing robotic-assisted mUKA with a preoperative computed tomography (CT) scan (image-based).

# Materials and Methods

We retrospectively reviewed 103 patients who underwent UKA at a single institution in our Institute performed by three expert surgeons in robotic-assisted surgery between September 2021 and December 2022.

We excluded patients who received an imaging-less, robotic-assisted surgery including only patients who underwent an image-based (CTscan) robotic-assisted surgery. Patients with incomplete data or who did not give consent to be part of a retrospective study were also excluded ( $\blacktriangleright$ Fig. 1).

All surgical procedures were performed by using the MAKO® robotic assistance (Stryker®, Mahwah) with the patient in a supine position, and a tourniquet was routinely inflated before making the skin incision. The same fixedbearing metal-backed cemented unicompartmental knee prosthesis was implanted (RESTORIS MCK Partial Knee, Stryker, Mahwah) with the assistance of the MAKO Robotic system.

#### Data Acquisition

The patients had received preoperative CT scans as standard of care, in order to plan the surgical procedure. The CT scans were all obtained under the same protocol (200 mA, 120 kV, slice spacing 0.625 mm, in-plane pixel resolution 0.488 mm), corresponding to the requirements for a robotic TKA system (Mako; Stryker, Mahwah, NJ), and included the hip, knee, and ankle. A single MAKO Product Specialist segmented the CT scans and reconstructed the 3D geometry of the tibia and fibula. In the axial plane, a circle was placed with contact on the posteromedial cortical and approximately 4 mm from the posterolateral cortical, thus obtaining the first reference (►Fig. 2A). Subsequently, we positioned the circumference in



Fig. 1 Flowdiagram with exclusion criteria.



Fig. 2 (A–C) Center of the tibia calculated with MAKO Stryker software.

the coronal plane with contact to the medial and lateral cortical, thus obtaining the second reference (►Fig. 2B). Finally, the third reference was obtained by positioning the circumference in the sagittal plane in contact with the anterior and posterior cortical (►Fig. 2C). The threecentral points of the obtained circumferences allowed us to obtain the center of the knee. Therefore, the IMAwas obtained as the axis of the best-fit cylinder to the periosteal cortex of the proximal tibia, between the most distal cross-section on the CT scan at the knee level and the distal end of the tibial tubercle. At least 130 mm of the proximal tibial shaft was utilized to define the IMA. TheTMA was defined according to industry standards as the line connecting the center of the ankle with the center of the knee. The center of the ankle was defined as the intermalleolar point located at 44% of the intermalleolar distance from the medial malleolus. After defining our reference points (center of the knee, anatomical axis, center of the ankle, and TMA), the Mako protocol allows us to calculate the tibial slope in relation to the dedication of the anatomical ( $\blacktriangleright$ Fig. 3A) or TMA ( $\blacktriangleright$ Figs. 3B and 4).

#### **Statistics**

Two orthopaedic surgeons measured the angular difference between the anatomic axis and the TMA. Differences were reported as negative when the anatomic axis was anterior to the TMA, resulting in a reduction of the posterior slope. We then summarized the difference between both axes as the mean and standard deviation.

Statistical analysis was performed through Prism 9.4 (GraphPad Software, Boston, MA). The Shapiro–Wilk test was used to analyze the normality of the distributions. Descriptive statistics (means, standard deviations [SDs], ranges as appropriate) were reported to explain the data. The measurements noted from the different methods were compared using the Wilcoxon matchedpairs signed-rank test. The difference of between males and females was measured using the Mann–Whitney U test. Statistical significance was set as  $p$ -values  $< 0.05$ .

# Results

Following the exclusion criteria, we extracted data from 67 patients. In total, 38 men and 29 women were included in the retroprospective analysis, with an age range between 47 and 69 years (mean 62 years) and a body mass index rangebetween 20 and 36 kg/m<sup>2</sup> (mean 28). Clinical data for all patients are shown in ►Table 1.

In 58 of the 67 knees, the IMA was anterior to the TMA, resulting in an apparent reduction of the PTS on radiographic measurements compared to MAKO CT measurements with the TMA. Considering the overall population ( $n = 67$ ), we observed a statistically significant difference between the



Fig. 3 (A) Slope calculated with the intramedullary axis.(B) Slope calculated with transmalleolar axis.



Fig. 4 Simplified image of the use of axes for slope calculation using CT with Mako protocol. Blue denotes the transmalleolar axis and red, the intramedullary axis.





Abbreviations: BMI, body mass index; SD, standard deviation.

measurement of the Transmalleolar Group (mean value  $\pm$ SD;5.48  $\pm$  0.87) and the Intramedullary Group (3.6  $\pm$  1.57), with  $p < 0.0001$  ( $\blacktriangleright$  Fig. 5A). The difference between both axes was  $1.9 \pm 1.8$  degrees(average  $\pm$ SD) and ranged from 6.2 to 2.7 degrees, with negative values corresponding to anIMA anterior to the TMA. Furthermore, in nineknees, the slope was increased. The reduction of the slope was <2 in 27 knees, representing 40% of the cohort; between 2 and 4 in 23 knees, representing 34% of the cohort; between 4 and 6 in 7 knees, representing 10% and one knee over 6 ( $\blacktriangleright$  Fig. 6).

In the male population ( $n = 38$ ), the difference between the groups was also significant with  $p < 0.0001$ : Transmalleolar Group  $(5.46 \pm 0.92)$  and the Intramedullary Group  $(3.67 \pm 1.39; \rightarrow$ Fig. 5B). Similarly, for the female population  $(n = 29)$  the difference was significant  $(p < 0.0001)$ : Transmalleolar Group (5.51  $\pm$  0.83) and the Intramedullary Group  $(3.5 \pm 1.8; -$ Fig. 5C).

Finally, comparing the differences between the two methods for males (1.79  $\pm$  1.78) and females (2.01  $\pm$  1.83), we did not observe a statistically significant difference, with  $p = 0.5649$  ( $\blacktriangleright$ Fig. 5D).

## **Discussion**

In our study, we found that the traditional IMA was 1.9 degreesanterior on the sagittal plane to the TMA; as such, setting PTS from the TMA during a robotic UKA may lead to an average of approximately 2degrees less PTS in situations where surgeons who are new to the use of MAKOassisted technology and are accustomed to slope calculation on X-rays and therefore accustomed to the use of the IMA. The surgeons, implant designers, and robotic/computer navigation system designers should be aware of this difference as the accuracy and reliability of computer-navigated and robotic devices can only be as good as the reference plans and predetermined targets. We reported that referencing the TMA rather than the IMA to set the PTS leads to 2degrees less PTS. As the fibula and therefore lateral malleolus are more posterior structures, the TMA lies posterior to the IMA of the tibia. The angular difference between the sagittal intramedullary and transmalleolar axes was 2degrees in the majority (40%) of patients; however, in 11% of patients, the angular difference was more than 4degrees, which could have significant clinical implications. Although we do not yet know the ideal PTS for each knee design and each patient, significant variations in planned tibial slope to achieve tibial slope can have significant kinematic implications in primary UKA where mechanical alignment concepts are used and for surgeons who are approaching the use of robot-assisted technologies for the first time.

The best technique to measure the PTS on lateral X-rays is still debated in the literature, and there is no consensus on the best method. The most commonly used procedure is a combination of four different methods used in previous studies.<sup>19</sup> The tangent to the MTP is considered the proximal reference line in all four measurement methods. On the lateral X-rays, the line connecting the top highest anterior and posterior points of the medial plateau was taken into account as the stable line for the tibial slope. As for the second reference line, four different lines perpendicular to one of the anatomic lines which all have been used in earlier studies were selected: (1) anterior tibial cortex line, (2) proximal tibial anatomic axis (PTAA), (3) posterior tibial cortex line, and (4) proximal fibular anatomic axis (PFAA; ►Fig. 7). For all anatomic reference line drawings, a starting point at the level of 15 cm below the joint line convenient for each reference line and a second reference point 5 cm below the tibial tuberosity were used. For PTAA



Fig. 5 (A-D) Graphical representation of the statistical results obtained.



Fig. 6 The slope difference takes a negative value when the intramedullary axis is anterior to the transmalleolar axis. The table groups the patients analyzed in relation to a range of slope differences.

and PFAA, the middle points of the tibia and fibula, respectively, at these levels were defined as starting and passing points. The angle between the tangent to the medial plateau and each perpendicular line to the selected anatomic line was measured as the tibial slope. Since the normal anatomic tibial slope is in a posterior and downward direction, PTS values were defined as positive  $(+)$ , and anterior slope values were defined as negative  $(-)$ .

The ACL deficiency was included in the relative contraindications for UKA, however, Boissonneault et al proposed that a functionally intact ACL is not always an essential prerequisite for a successful UKA.<sup>15</sup> To improve stability in the ACL-deficient knee, the PTS may be reduced<sup>20</sup> resulting in a comparable femoral rollback to healthy knees<sup>21</sup> and a more stable knee in flexion.<sup>14</sup> When approaching a patient with monocompartimental arthrosis in ACL-deficient knees,



Fig.7 Four different methods of measuring tibial slope: anterior tibial cortex (ATC), proximal tibial anatomic axis (PTAA), posterior tibial cortex (PTC), and proximal fibular anatomic axis (PFAA).

the main features to take into account are the patient's biological age, functional demands, and primary symptoms.

The importance of knowing a reliable and accurate system to measure PTS is important because it may affect the knee function of UKA in patients candidate for this procedure but with an ACL insufficiency. However, slope correction is not the only technique that may enlarge the indications ofUKA in patients with ligament deficiency. Indeed, the possibility to perform an ACL reconstruction combined with mUKA is  $\frac{1}{4}$ considered<sup>14,15,20,21</sup> but the age and functional activity still play a significant role in our decision. Elderly patients with lower functional requests may benefit from the UKA without ACL reconstruction. On the other hand, in younger patients with isolated monocompartimental arthrosis, an ACL reconstruction, regaining stability in their knee, is preferred. In the subjective evaluation of these patients, mechanical pain is usually present due to monocompartimental arthrosis, eventually associated with a swollen knee. On the other hand, instability, even if ACL is deficient, may not be referred to as a main symptom, probably because of the muscular status, the functional requests, or the presence of posterior osteophytes and capsule stiffness, which contribute to knee stability. In those patients, ACL reconstruction may not be performed to avoid further surgical steps and increasearthrofibrosis risk.

In the literature, authors comparing patients who underwent medial UKA with patients with a medial UKA, presenting ACL deficiency reported no differences in kinematics and kinetics, including knee joint moments.<sup>22</sup>According to theliterature, we feel confident to say that UKA combined with ACL reconstruction is a preferable treatment option in young and active patients with ACL deficiency and bone-on-bone

medial compartment arthritis. Simultaneous or staged ACL reconstruction, although making the procedure more complex, tends to provide superior outcomes, in particular in younger and more active patients.<sup>23</sup> However, in elderly, with isolated UKA, correcting the PTS, without ACL reconstruction may be a reasonable and attractive option.<sup>23</sup> Of note, some studies stated that the maximum contact stresses on the PE insert and lateral articular cartilage as well as the quadriceps force in normal and varus knee mUKA Finite Element models with ACL deficiency were significantly increased in the stance phase of the gait cycle, as compared with those in a mUKA model without ligamentous deficiency.<sup>24,25</sup> The stance phase of gait begins when the foot first touches the ground and ends when the same foot leaves the ground. This finding further confirmed the importance of patient selection because performing medial UKA in the presence of instability due to ligamentous deficiency could result in an increase in contact stresses on the PE insert and lateral articular cartilage, leading to early implant loosening.<sup>24,25</sup>

It is important to know how to calculate the slope and which reference points to use, both in preoperative and postoperative planning. This allows us to modify the result in case of patients with anterior or posterior instability, such as cruciate ligament injured knees. As already expressed, for young patients there is an indication to perform mUKA and ACL reconstruction, while in older patients the performance of mUKA with slope variation to improve anteroposterior stability plays an essential role. mUKA with a PTS reduction, compared to the native knee, may be an alternative treatment option for carefully selected patients. In these cases, it is essential to have a proper reference to calculate and define the slope pre-, intra-, and postoperatively.

The present study comes with several limitations. First, this is a radiographic study of a small number of patients undergoing primary robotic UKA at a single institution. For this study, we assumed that since both robotic and computer-navigated UKA techniques reference the TMA intraoperatively they would yield similar results, and the effect would be similar. Furthermore, as this was a radiographic study for proof of concept, we did not correlate variations in slope with range of motion, knee kinematics, or clinical outcomes. Computernavigated or robotic UKA that references the TMA may result in twomore PTSs on the tibial component than if the traditional tibial IMA was referenced. As such, we recommend that surgeons add 1.5 to 2 PTSs in order to achieve the desired PTS on the IMA of sagittal postoperative radiographs and prevent no correct sloping tibial components. Implant designers and designers of computer-navigated and robotic-assisted devices for primary UKA should also be aware of the angular difference between the tibial IMA and the TMA when establishing references during navigated UKA.

# Conclusions

Tibial components implanted with the help of a CT scanbased preoperative planning MAKO will show an average of 1.9 degrees more than those measured on sagittal radiographs potentially of concern for knee kinematics. A

universal language is needed to standardize the slope calculation and the respective reference axis used.

#### Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of "Azienda Ospedaliero Universitaria Careggi."

### Patient Consent

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

#### Authors' Contributions

Conceptualization, M.I. andM.C.Methodology, M.C. and M.I. Software,L.Z. Validation,M.A. Formal analysis, M.A. Investigation, M.A. Resources, M.I., C.C., and R.C. Data curation, M.I. and M.C.Writing—original draft preparation, M.C., M.I., and L.Z. Writing—review and editing, M.C., L.Z., and M.I. Visualization,M.A.Supervision, C.C. andR.C.Project administration, M.I. andR.C. All authors have read and agreed to the published version of the manuscript.

#### Data Availability

Suggested data availability statements are available in the section, "MDPI Research Data Policies," at [https://www.](https://www.mdpi.com/ethics) [mdpi.com/ethics.](https://www.mdpi.com/ethics)

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# Conflict of Interest

None declared.

## **References**

- 1 Mittal A, Meshram P, Kim WH, Kim TK. Unicompartmental knee arthroplasty, an enigma, and the ten enigmas of medial UKA. J Orthop Traumatol 2020;21(01):15
- 2 Argenson JNA, Parratte S, Bertani A, Flecher X, Aubaniac JM. Longterm results with a lateral unicondylar replacement. ClinOrthop Relat Res 2008;466:2686–2693
- 3 Flecher X, Parratte S, Aubaniac JM, Argenson JNAA. A 12–28-year follow-up study of closing wedge high tibial osteotomy. ClinOrthopRelated Res 2006;452:91–96
- 4 Parratte S, Argenson JNA, Pearce O, Pauly V, Auquier P, Aubaniac JM. Medial unicompartmental knee replacement in the under-50s. J Bone Joint Surg Br 2009;91(03):351–356
- 5 Siman H, Kamath AF, Carrillo N, Harmsen WS, Pagnano MW, Sierra RJ. Unicompartmental knee arthroplasty vs total knee arthroplasty for medial compartment arthritis in patients older than 75 years: comparable reoperation, revision, and complication rates. J Arthroplasty 2017;32(06):1792–1797
- 6 Johal S, Nakano N, Baxter M, Hujazi I, Pandit H, Khanduja V. Unicompartmental knee arthroplasty: the past, current controversies, and future perspectives. J Knee Surg 2018;31(10):992–998
- 7 Newman J, Pydisetty RV, Ackroyd C. Unicompartmental or total knee replacement: the 15-year results of a prospective randomised controlled trial. J Bone Joint Surg Br 2009;91(01):52-57
- 8 Griffin T, Rowden N, Morgan D, Atkinson R, Woodruff P, Maddern G. Unicompartmental knee arthroplasty for the treatment of unicompartmental osteoarthritis: a systematic study. ANZ J Surg 2007;77(04):214–221
- 9 Burn E, Sanchez-Santos MT, Pandit HG, et al. Ten-year patientreported outcomes following total and minimally invasive unicompartmental knee arthroplasty: a propensity score-matched cohort analysis. Knee Surg Sports Traumatol Arthrosc 2018;26 (05):1455–1464
- 10 Noticewala MS, Geller JA, Lee JH, Macaulay W. Unicompartmental knee arthroplasty relieves pain and improves function more than total knee arthroplasty. J Arthroplasty 2012;27(8 Suppl):99–105
- Price AJ, Dodd CAF, Svard UGC, Murray DW. Oxford medial unicompartmental knee arthroplasty in patients younger and older than 60 years of age. J Bone Joint Surg Br 2005;87(11): 1488–1492
- 12 Barbadoro P, Ensini A, Leardini A, et al. Tibial component alignment and risk of loosening in unicompartmental knee arthroplasty: a radiographic and radiostereometric study. Knee Surg Sports Traumatol Arthrosc 2014;22(12):3157–3162
- 13 Maudhuit B, Le P. The causes of failures in unicondylar knee arthroplasties. Eur J Orthop Surg Traumatol 1995;5(03):226–235
- 14 Engh GA, Ammeen DJ. Unicondylar arthroplasty in knees with deficient anterior cruciate ligaments knee. ClinOrthop Relat Res 2014;472:73–77
- 15 Boissonneault A, Pandit H, Pegg E, et al. No difference in survivorship after unicompartmental knee arthroplasty with or without an intact anterior cruciate ligament. Knee Surg Sports Traumatol Arthrosc 2013;21(11):2480–2486
- 16 Suggs JF, Li G, Park SE, Steffensmeier S, Rubash HE, Freiberg AA. Function of the anterior cruciate ligament after unicompartmental knee arthroplasty: an in vitro robotic study. J Arthroplasty 2004;19(02):224–229
- 17 Zee MJM, Keizer MNJ, Dijkerman L, van Raaij JJAM, Hijmans JM, Diercks RL. The correlation between posterior tibial slope and dynamic anterior tibial translation and dynamic range of tibial rotation. J Exp Orthop 2021;8(01):71
- 18 Franz A, Boese CK, Matthies A, Leffler J, Ries C. Mid-term clinical outcome and reconstruction of posterior tibial slope after UKA. J Knee Surg 2019;32(05):468–474
- 19 Çullu E, Aydoğdu S, Alparslan B, Sur H. Tibial slope changes following dome-type high tibial osteotomy. Knee Surg Sports Traumatol Arthrosc 2005;13(01):38–43
- 20 Giffin JR, Vogrin TM, Zantop T, Woo SLY, Harner CD. Effects of increasing tibial slope on the biomechanics of the knee. Am J Sports Med 2004;32(02):376–382
- 21 Suero EM, Citak M, Cross MB, Bosscher MRF, Ranawat AS, Pearle AD. Effects of tibial slope changes in the stability of fixed bearing medial unicompartmental arthroplasty in anterior cruciate ligament deficient knees. Knee 2012;19(04):365–369
- 22 Suter L, Roth A, Angst M, et al. Is ACL deficiency always a contraindication for medial UKA? Kinematic and kinetic analysis of implanted and contralateral knees. Gait Posture 2019; 68:244–251
- 23 Mancuso F, Dodd CA, Murray DW, Pandit H. Medial unicompartmental knee arthroplasty in the ACL-deficient knee. J Orthop Traumatol 2016;17(03):267–275
- 24 Kwon HM, Kang KT, Kim JH, Park KK. Medial unicompartmental knee arthroplasty to patients with a ligamentous deficiency can cause biomechanically poor outcomes. Knee Surg Sports Traumatol Arthrosc 2020;28(09):2846–2853
- 25 Zumbrunn T, Schütz P, von Knoch F, Preiss S, List R, Ferguson SJ. Medial unicompartmental knee arthroplasty in ACL-deficient knees is a viable treatment option: in vivo kinematic evaluation using a moving fluoroscope. Knee Surg Sports Traumatol Arthrosc 2020;28(06):1765–1773