Appendix E1

Search Strategy for Determining DVT Cases

Given that the vast majority of these reports were expected to be negative, the following most common phrases associated with negative reports were searched and used to exclude cases:

“Right lower extremity: No evidence of deep venous thrombosis above the knee. Left lower extremity: No evidence of deep venous thrombosis above the knee.” “No evidence of deep venous thrombosis.” “No evidence of deep venous thrombosis in the right lower extremity veins above the knee.” “No evidence of deep venous thrombosis in the right lower extremity above the knee.” “No evidence of deep venous thrombosis in the lower extremity veins in either leg above the knee.” “No evidence of deep venous thrombosis in the left upper extremity.” “No evidence of deep venous thrombosis in the left lower extremity veins above the knee.” “No evidence of deep venous thrombosis in the left lower extremity above the knee.” “No evidence of deep venous thrombosis in the bilateral lower extremity veins above the knee.” “No evidence of deep venous thrombosis in the bilateral lower extremities above the knees.” “No evidence of deep venous thrombosis in the bilateral lower extremities above the knee.” “No evidence of deep venous thrombosis in left or right lower extremity veins above the knees.” “No evidence of deep venous thrombosis in either lower extremity veins above the knees.” “No evidence of deep venous thrombosis in either lower extremity above the knee.” “No evidence of deep venous thrombosis in the left lower extremity veins above the knee.” “No evidence of deep vein thrombosis in bilateral lower extremities above the knees.” “No evidence of deep vein thrombosis bilateral lower extremities.” “1. No evidence of deep venous thrombosis in the right upper extremity veins as above.” “1. No evidence of deep venous thrombosis in the left upper extremity veins as above.” “1. No evidence of deep venous thrombosis in the right lower extremity veins above the knee.” “1. No evidence of deep venous thrombosis in the right lower extremity above the knee. 2. Patent bilateral iliac veins.” “1. No evidence of deep venous thrombosis in the left lower extremity veins above the knee.” “1. No evidence of deep venous thrombosis in the left lower extremity above the knee. 2. Patent bilateral iliac veins.” “1. No evidence of deep venous thrombosis in the bilateral lower extremities above the knee. 2. Patent bilateral iliac veins.” “1. No evidence of deep venous thrombosis in right lower extremity above the knee. 2. Patent bilateral iliac veins.” “1. No evidence of deep venous thrombosis in left lower extremity above the knee. 2. Patent bilateral iliac veins.” “1. No evidence of deep venous thrombosis in either lower extremity veins above the knees.” “1. No evidence of deep venous thrombosis in either lower extremity above the knee. 2. Patent bilateral iliac veins.” “1. No evidence of deep venous thrombosis in bilateral lower extremities above the knees.” “1. No evidence of deep venous thrombosis in bilateral lower extremities above the knee. 2. Patent bilateral iliac veins.” “1. No evidence of deep venous thrombosis in the right lower extremity veins above the knee.” “1. No evidence of deep venous thrombosis in the left lower extremity veins above the knee.” “1. No evidence of deep vein thrombosis in bilateral lower extremities above the knees. IMPRESSION.” “1. No evidence of deep vein thrombosis in bilateral lower extremities above the knees.” “1. No evidence of deep vein thrombosis in bilateral lower extremities above the knee.”

Next, phrases associated with positive DVT were used to search the remaining reports to find the positive DVT cases: “*Thrombosis*”or like”*DVT*”or like”*nonocclusive*”or like”*thrombus*”or like”*clot*”or like”*occlusive*”or like”*non-occlusive*”or like

”*thromboses*” or like "*deep venous thrombosis*" or like "*clot*" or like "*thrombosis*" or like "*dvt*" or like "*filling defect*" or like "*thrombus.*"

Appendix E2

Theoretical Construct for Determining Which Vessels Should Be Measured

LCIV compression was the major exposure that was assessed, and we tested the hypothesis that LCIV compression is more frequent in cases with left DVT than in control subjects with right DVT, on the basis of the belief that DVT on the left is often caused by compression of the LCIV by the right common iliac artery (RCIA). This compression results in venous stasis, and the repetitive pulsation of the RCIA over the vein causes localized trauma. In turn, the localized trauma leads to the formation of venous webs and spurs. Venous stasis and venous spurs and/or webs are hypothesized to predispose patients to left-sided DVT. To assess this construct, we may hypothesize several different types of measurements that may capture both or at least one of the relevant constructs of interest: stasis and venous webs and/or spurs.

Stasis

Stasis refers to the impairment of flow; in this case, the impairment of blood flow from the left lower extremity due to the compression of the LCIV. Components of volume flow rates, such as velocity and cross-sectional area, may be assessed to serve as surrogate measures for volume flow. Like volume flow rates, velocity measurements would require imaging studies such as CT angiography, MR angiography, or percutaneous studies that few patients are likely to undergo. The cross-sectional area of a vessel, however, may be assessed by measuring vessel radius, which is available on cross-sectional images such as pelvic CT scans and MR images. Many more patients with DVT might be expected to undergo CT or MR imaging; hence, this group of patients would enable us to have enough of a sample size for our study to be adequately powered while providing us with relevant information regarding our construct of interest.

Venous Webs and/or Spurs

Historically, venous spurs and/or webs have been diagnosed by means of autopsies in which vein segments were harvested and analyzed for the presence or absence of lesions at the location where the RCIA crosses the LCIV. The measurement of iliac vein diameters may serve as a surrogate for the formation of venous spurs and/or webs in those patients with iliac vein compression; we hypothesize that individuals with compressed iliac vein diameters will be more likely to have venous webs and/or spurs.

Method of Measuring Exposure

The diameter of the LCIV was assessed by two board-certified radiologists who selected the diameter of the LCIV at the maximal point of compression from the RCIA and noted the section on which maximal compression is noted. Readers were instructed to measure the diameter of the vessel once the section on which maximal compression was present was determined. To determine in which orientation of the vessel we would want to make the measurements, we considered possible geometries of the LCIV and the ensuing measurements that we may want to make to make accurate measurements of the iliac vein.

If we consider all of these possible orientations of the LCIV, then the only measurement that accurately and consistently measures the iliac vein diameter is the measurement of the minor diameter of the iliac vein, assuming that the CT sections yield an image of an ellipse.

Percentage compression may be determined by using several different types of measurements. Once the minor diameter of the LCIV is determined at the section showing maximal compression, percentage compression may be determined by dividing this value by the average of the minor diameter of the LCIV proximal to the point of compression and that distal to the point of compression. In addition, percentage compression may be obtained by dividing the diameter of the compressed LCIV by the diameter of the RCIV at the same level. Advantages and disadvantages of each measurement will be discussed.

Regarding the proximal LCIV as the denominator for iliac vein compression, we noted in our pilot study that measurements of the proximal LCIV were unreliable and difficult to assess, particularly for those patients in whom maximal compression of the LCIV occurred very close to the bifurcation of the inferior vena cava. Hence, we did not ask readers to make this measurement in our final data-entry form.

Regarding the distal LCIV as a measurement for percentage compression of the LCIV, a question arose as to where the measurement should be made—from the point of compression all the way to the bifurcation of the LCIV into the external and internal iliac veins.

In our pilot study, we did not provide readers with any specific instructions on where the measurements should be made so that readers would be allowed to come up with different methods to assess iliac vein diameters. Among several different possible locations for where the iliac vein should be measured, the readers decided that the distal measurement of the LCIV should be made immediately prior to the bifurcation of the LCIV into the external and internal iliac veins. The advantages of this measurement include the fact that the measurement represents a consistent instruction that can be asked of any radiologist in this study and in future studies and that aside from RCIA compression, the vein is expected to remain identical in diameter from the origin of the vessel from the bifurcation of the inferior vena cava all the way down to the bifurcation of the common iliac vein into the external and internal iliac vein, as long as there are no collateral vessels coming off the common iliac vein.

In a similar fashion, the diameter of the RCIV may be measured at any point from the bifurcation of the inferior vena cava to the bifurcation of the RCIV. For the purpose of consistency, the RCIV was measured immediately prior to the bifurcation of the RCIV. These measures can serve as an additional method of assessing iliac vein compression, particularly in the situation in which the left side might be compromised by the presence of proximal clot. One possible limitation of this measurement is that individuals may have natural asymmetries in the sizes of their iliac veins, which may cause either under- or overestimation of the percentage of iliac vein compression.

Appendix E3

Measurement Parameters

For each parameter, plots for reader 1 and reader 2 are presented separately. In addition, a plot with the averaged values of reader 1 and reader 2 is presented. For averaged values, the average of the first reading (computed by averaging reader 1's and reader 2’s first readings) was compared with the average of the second reading (computed by averaging reader 1's and reader 2’s second readings) to determine agreement statistics.

Intrapatient Variability

Fifteen case patients were selected for inclusion in the intrapatient variability study. The mean age of the case patients was 61.4 years (95% CI: 49.6, 73.2 years), and the mean time elapsed between examinations was 93.8 days (range, 5–326 days). (Tables E1 and E2) (Fig E1).

Interreader Variability

The 230 cases were read once by one reader and a second time by the other reader, allowing us to estimate interreader variability (Tables E3 and E4) (Fig E2).

Intrareader Variability

Thirty cases were selected at random for inclusion in the intrareader variability study. Both readers read the cases after reading the main study cases in the same order after approximately 3–4 months (Tables E5 and E6) (Fig E3).

Masking Substudy

In the initial phase of the study, readers were asked to indicate if they noted clot on the CT scans. If clot was noted in the LCIV, external iliac vein, common femoral vein, or femoral vein, these studies were included in the substudy and were considered as unmasked studies. Approximately 6 months later, the readers were presented only the section on which they had previously noted maximal compression of the LCIV; the other sections on which clot was noted were masked to the readers. This approach was utilized because it involved a comparison of identical CT scans read by the same reader, with the only difference being the presence or absence of clot on the scans. Although it is possible that readers may have been able to recall reading similar cases, thereby influencing their interpretations of the masked cases, the long delay between the interpretations of the initial studies and the current studies makes this possibility unlikely.

Mean differences in readings between masked and unmasked studies were computed with 95% CIs. These CIs were compared with 0 to determine if there was a statistically significant difference in masked and unmasked readings. To model the possibility that the effect of masking may differ by reader, mean differences in readings were compared for each reader by using *t* tests (Table E7) (Fig E4).

Qualitative Compression Rating Versus Quantitative Compression Rating

Quantitative compression levels were found to be associated with increasing levels of qualitative compression (none to severe) (Fig E5).

Appendix E4

In this study, we used our hypothesized causal model to guide our selection of confounders (14,15).

A priori, we may suspect risk factors that alter pelvic anatomy, such as pregnancy and abdominal aortic aneurysms, and left-sided unilateral findings, such as masses, fluid collections, surgical clips, stents, trauma, and lymphadenopathy, to be potential confounders. In several studies, pregnancy has been found to be highly associated with left-sided DVT, with DVT occurring as much as 75%–90% of the time on the left side (16). We hypothesize that in pregnancy, the growing fetus exacerbates compression of the LCIV by the RCIA and hence will be associated with the exposure. Pregnancy may also be associated with DVT in general through its effects on hypercoagulability or venous damage. However, we would not expect pregnancy to be associated with left-sided DVT independent of the pathway through LCIV compression, because most other structures and behaviors are symmetric.

Aside from LCIV compression, pregnancy is associated with bed rest and increased hypercoagulable factors (17). These risk factors would be expected to increase the risk of DVT, but they would not be expected to increase the risk of left-sided DVT versus right-sided DVT. Pregnancy may be associated with LCIV compression (exposure); however, it would not be expected to be associated with the outcome (left-sided DVT) by means of any other pathway besides LCIV compression. Hence, pregnancy aggravates the causal mechanism of interest rather than confounds it. Similarly, abdominal aortic aneurysms have been associated with decreased LCIV compression (18); however, we would not expect abdominal aortic aneurysms to be associated with left-sided DVT independent of their influence on LCIV compression. Hence, we would not expect abdominal aortic aneurysms to act as a potential confounder. Finally, unilateral risk factors include trauma, lymphadenopathy, clips, stents, masses, and fluid collections. Left-sided risk factors may influence LCIV compression; however, these risk factors would not be expected to influence the risk of left-sided DVT independent of any pathway besides LCIV compression. Right-sided unilateral findings are not expected to influence LCIV compression; hence, both left- and right-sided unilateral findings were not considered as potential confounders. This still leaves other behaviors or asymmetries that may relate to left- rather than right-sided DVT risk. Hypothetical examples could be behaviors such as driving, where legs are used differently, asymmetric seating, such as in airplane aisle versus window seats, or asymmetric constrictive devices (eg, gun holsters).

Generally, by using right-sided DVTs as controls for left-sided DVTs, we anticipate there will be no confounders, and our primary analysis will be unadjusted.

Appendix E5

Table of Sensitivity Analyses

To determine appropriate logistic regression models, LOWESS plots were generated for each of the three main methods of determining iliac vein compression (Fig E6).

On the basis of these models, cutpoints were determined for the logistic regression models and were used for the primary analyses (Table E8).

References

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