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The troubled course of the CHIVA Cure through clinical studies: a critical review

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Abstract

The treatment of Superficial Venous Insufficiency (SVI) encompasses a wide and disparate array of techniques, ranging from destructive procedures (endovascular ablation, stripping and sclerotherapy) to the conservative hemodynamic procedure (CHIVA). This variety of options betrays a wide degree of uncertainty on the recommended treatment, mainly due to technical biases in performing the CHIVA Cure that heavily affect the results from Randomized Controlled Trials (RCTs). In fact, the authors of the last Cochrane Review (CR) on the CHIVA Cure disowned its superiority based on the results from five RCTs in which more than 200 of the overall 419 participants allocated to the CHIVA arm had actually received treatments other than the CHIVA Cure. Further, the Guidelines (GLs) from both the American and the European Society for Vascular Surgery recommend the CHIVA Cure only to vascular surgeons experienced with this technique, contradicting what is expected of a specialist, *i.e.* mastery of the treatment of diseases in his or her specialty. Finally, CRs and GLs do not take into any account the ethically relevant issue that destructive procedures, recommended for vascular surgeons not experienced in the CHIVA Cure, will fatally deprive the patient of the Great Saphenous Vein (GSV), which is the first-choice infra-inguinal graft for the treatment of severe peripheral artery disease and to ward off the severely disabling condition resulting from limb loss, when angioplasty/stenting is not feasible.

In this paper we review and discuss the RCTs, CRs, and GLs concerning the CHIVA Cure available at June 2023 on Medline and Cochrane Central databases.

The treatment of Superficial Venous Insufficiency (SVI) encompasses a wide and disparate array of techniques, ranging from destructive procedures, such as stripping, endovascular techniques, and sclerotherapy, to the conservative hemodynamic treatment known as CHIVA Cure.[1]

This variety of options is only partially justified by the multifaceted SVI clinical and hemodynamic presentation. Indeed, even the most deeply convinced supporters of the CHIVA Cure, under some peculiar, very limited circumstances, recommend the use of sclerotherapy, alone or in the context of the CHIVA Cure.[2] On the contrary, such a number of available techniques actually betrays a wide degree of uncertainty on the recommended treatment for SVI, mainly due to the relevant technical biases concerning the CHIVA strategy and, sometimes, even the CHIVA tactic, heavily affecting the results from the Randomized Controlled Trials (RCTs) that have included the CHIVA Cure. As a consequence, the conclusions from the Cochrane Reviews (CRs) on the CHIVA Cure are, unavoidably, unreliable, and the recommendations from the Guidelines (GLs) on the treatment of SVI are misleading.

In this paper, we review and discuss the RCTs, CRs, and GLs concerning the CHIVA Cure available as of June 2023 on Medline and Cochrane Central databases.

Indeed, only five RCTs including the CHIVA Cure are available,[3-7] with overall 419 limbs allocated to the CHIVA arm. Of these, three RCTs,[3-5] with overall 293 limbs allocated to the CHIVA arm, have compared the CHIVA Cure with stripping and were included in the previous Cochrane Review,[8] and other two RCTs,[6,7] with overall 126 limbs allocated to the CHIVA arm, one comparing the CHIVA Cure with stripping and with Endovenous Laser Ablation (EVLA),[6] and one comparing the CHIVA Cure with stripping and with Radiofrequency Ablation (RFA),[7] have been added in the last Cochrane Review.[9]

Iborra-Ortega *et al.*[3] compared the five-year results in 49 participants undergoing stripping and 51 participants undergoing the CHIVA Cure. The authors found no significant difference with regard to clinical recurrences between the two groups (28.5% and 36% in the CHIVA and in the stripping arm, respectively), a high rate of Greater Saphenous Vein (GSV) thrombosis, only in the CHIVA arm (25.5%, $p<0.001$), a high rate of saphenous nerve injury, only in the stripping arm (22.4%, $p<0.001$), and a significantly shorter time of working difficulties in the CHIVA arm (7.8 *vs* 19.2 days, $p <0.001$).

Carandina *et al.*[4] compared the ten-year results in 75 participants undergoing stripping and 75 participants undergoing the CHIVA Cure. Authors found a significantly lower rate in the CHIVA arm of both clinical recurrences, assessed by the Hobbs' score,[10] (1.9±SE, $p=0.09$ *vs*

2.2±SE 0.12, p=0.038,) and instrumental recurrences, considered as a binary outcome, (18.5% *vs* 35%, p=0.041). No significant difference was found with regard to recurrences from the Saphenous-Femoral Junction (SFJ). Interestingly, authors found instrumental recurrences due to reflux from the GSV trunk to a varicose incompetent GSV tributary only in the CHIVA arm (18.5%, p<0.01) and recurrences without any demonstrable escape point only in the stripping arm (22%, p<0.01).

Pares *et al.*[5] compared the five-year results in 167 participants undergoing Stripping with Clinical Marking (S-CM), 167 participants undergoing Stripping with Duplex Marking (S-DM), and 167 participants undergoing the CHIVA Cure. The authors found a significantly lower rate in the CHIVA arm of both clinical recurrences, considered as "failure" according to Hobbs' classification,[10] (31.1%, *vs* 52.7%, *vs* 47.9%, in the CHIVA arm, in the S-CM arm and in the S-DM arm, respectively, p<0.001), without significant differences between the S-CM and the S-DM arm, and instrumental recurrences (40.1% *vs* 68.3% *vs* 61.15, in the CHIVA arm, in the S-CM arm and in the S-DM arm, respectively, p<0.001), without significant differences between the S-CM and the S-DM arm. As to postoperative complications, authors reported a significantly lower rate in the CHIVA arm of both bruises (46% *vs* 75% *vs* 69%, in the CHIVA arm, in the S-CM arm, and in the S-DM arm, respectively, p<0.001), and saphenous nerve injury (0% *vs* 5.8% *vs* 3.8%, in the CHIVA arm, in the S-CM arm and in the S-DM arm, respectively, p<0.012). Finally, the CHIVA arm also showed a significantly shorter time of working difficulties (5.3 *vs* 20.8 *vs* 17.6 days, in the CHIVA arm, in the S-CM arm, and in the S-DM arm, respectively, p<0.001).

Wang et *al.*[6] compared the 18-month results in 50 participants undergone stripping, 50 participants undergone EVLA and 50 participants undergone the CHIVA Cure. The authors found a significantly lower rate of clinical recurrences in the CHIVA arm with respect to the stripping arm (0% *vs* 20%, p<0.001) and no significant difference with respect to the EVLA arm (0% *vs* 6.25%, p=NS). As a whole, the CHIVA arm showed a significantly lower rate of postoperative complications, such as thrombosis, bruising, nerve injury, and wound infections, (6% *vs* 38% *vs* 30% in the CHIVA arm, in the stripping arm and in the EVLA arm, respectively, p<0.05).

Gonzàles-Cañas *et al.*[7] compared the two-year results in 75 participants undergoing stripping, 74 participants undergoing RFA, and 76 participants undergoing the CHIVA Cure. The authors found a significantly higher rate in the CHIVA arm of both clinical recurrences, according to the REVAS classification,[11] (14.7%, *vs* 7.2%, *vs* 4.3%, in the CHIVA arm, in the RFA arm and in the stripping arm, respectively, p<0.001) and instrumental recurrences (46.7% *vs* 13% *vs*

7.1%, in the CHIVA arm, in the RFA arm and in the stripping arm, respectively, p<0.001). However, of the 35 (46.7%) instrumental recurrences found in the CHIVA arm, 11 (14.7%), corresponding to the 11 cases of clinical recurrences, were described as "neovascularization at the Saphenous-Femoral Junction (SFJ) and new pelvic vein", and the other 24 (32%) as "incompetent GSV without a drainage perforator". Finally, no significant difference concerning postoperative complications was found among the three groups.

Indeed, all the RCTs comparing the treatments for SVI are, unavoidably, at high risk of "detection" bias,[12] as instrumental outcome assessors are not blind with regard to the treatment the participant has undergone. In fact, during Duplex ultrasound examination the assessor can easily realize whether the greater saphenous vein has been actually removed, or it has been completely occluded, or it has been left in place and shows some flow, either anterograde or retrograde. The same "detection" bias also occurs, in most cases, for clinical outcome assessors who are not blind with regard to the treatment the participant has undergone, simply by looking at the scars resulting from the operation. Further, all the RCTs comparing the treatments for SVI are also, unavoidably, at high risk of "performance" bias,[12] as both participants and personnel are not blind with regard to the assigned treatment arm.

With respect to the previous CR,[8] the last CR[9] on the CHIVA Cure has included two more RCTs[6, 7] that, along with sharing the (unavoidable) high risk of "detection" and "performance" biases, are also both at high risk of the (avoidable) "reporting" bias,[12] the former[6] because the authors did not explain the outcomes suitably in the methods section,[9] and the latter[7] because the authors changed the primary outcome specified in the protocol and randomized seven participants twice.[9] Further, the two added RCTs also showed a relevantly shorter follow-up (18 months[6] and two years[7] *vs* five years[3,5] and 10 years,[4] which favours destructive procedures, as recurrences, particularly the clinical ones, are generally more late compared to the CHIVA Cure. Thus, it is not surprising that the last CR[9] has downgraded the grade of evidence concerning the CHIVA Cure, which was "moderate-certainty" in the previous review,[8] to "low-certainty", and has disowned its superiority, concluding that: "a) there may be little or no difference in the recurrence of varicose veins when comparing CHIVA to stripping, but CHIVA may slightly reduce nerve injury and hematoma; b) CHIVA may make little or no difference to recurrence compared to radio frequency ablation, but may result in more bruising, c) CHIVA may make little or no difference to recurrence and side effects compared to endovenous laser therapy".

However, the last CR,[9] although masterfully conducted in terms of methodology, did not take into any account the relevant technical biases shown by the RCTs concerning both the

CHIVA strategy and, sometimes, even the CHIVA tactic, which are, definitely, the most severe pitfalls against the CHIVA Cure. In fact, a part from the RCT conducted by Carandina *et al.*[4] (75 participants), in the remaining four RCTs[3,5-7] more than 200 of the 344 participants allocated to the CHIVA arm actually received procedures other than the CHIVA Cure.

As this is the most critical issue, an in-depth recap of the basic knowledge of the CHIVA Cure is absolutely needed.

In terms of hemodynamics, the vast majority of patients with primary varicose veins in the territory of the GSV show either a type I venous-venous shunt (20-30%), *i.e.* a shunt with the escape point located at the SFJ and the re-entry perforator vein located on the GSV trunk, or a type III venous-venous shunt (60-70%), *i.e.* a shunt with the escape point located at the SFJ but with the re-entry perforator vein located on an incompetent GSV tributary.[13] For type I shunts, the treatment of choice is the "one-time surgery", also known as CHIVA 1 strategy, *i.e.* the disconnection of both the escape point, by performing a "crossotomy" instead of the more traditional "crossectomy", and the incompetent GSV tributaries at the same time.[13-16] This results in a "draining" GSV, *i.e.* a GSV which receives the blood from SFJ collaterals and the competent GSV tributaries left connected to the GSV, and drains into the deep venous system through the re-entry perforator vein located on the GSV trunk, fully fulfilling the "hemodynamic" (H) aspect that characterizes the CHIVA Cure. On the contrary, in type III shunts the "one-time surgery" results in a "non-draining" GSV, as the re-entry perforator vein located on the incompetent GSV tributary has been disconnected from the GSV, so that the blood from SFJ collaterals and the competent GSV tributaries left connected to the GSV cannot adequately drain into the deep venous system. Obviously, this kind of surgery cannot be considered as a CHIVA procedure as the "hemodynamic" (H) aspect that characterizes the CHIVA Cure has not been fulfilled.[13-16] Further, the "one-time surgery" in type III shunts often results in GSV thrombosis, which, although the SFJ is closed and there is no risk of pulmonary embolism, is, anyhow a very unstable and evolutive condition.[15,16] Thus, for type III shunts it has been suggested to perform a "two-time surgery", also known as CHIVA 2 strategy,[14] in which the first surgical gesture is the disconnection of the GSV tributary where the re-entry perforator vein is located. For safety reasons, as such a procedure leaves the SFJ open, it should not be performed on GSV whose caliber is > 10mm, given the risk of GSV thrombosis and the consequent risk of pulmonary embolism.[14] The first surgical gesture of the CHIVA 2 strategy is aimed at re-modelling the GSV hemodynamics by promoting the development of a re-entry perforator vein located on the GSV trunk, as in type I shunts. The re-appearance of a GSV reflux over the follow-up suggests that a re-entry GSV perforator vein has developed and that

the patients is ready to undergo the second surgical gesture, *i.e.* the crossotomy, without resulting any more in a "non-draining" GSV. Sometimes, the re-appearance of a GSV reflux over the follow-up may also be due to a "jump" of the previous ligature of the incompetent GSV tributary where the re-entry perforator vein was located, which means that the aim of the first surgical gesture of the CHIVA 2 strategy has failed, and that we need to re-address the problem (a detailed description on how to manage the problem is beyond the scope of this paper). Finally, with regard to the CHIVA tactic, the most critical issue concerns the surgical gesture on the SFJ, and it is represented by the correct positioning of the metallic clip, that should be really flush with and actually pinch the femoral vein wall, along with the closure of the *fossa ovalis* with a non-absorbable suture, both to prevent the occurrence of SFJ recurrences.

That being said, in all the RCTs[3-7] included in the last CR on the CHIVA Cure,[9] the participants allocated to the CHIVA arm were treated by the "one-time surgery". However, in the RCT conducted by Carandina *et al.*[4] only participants showing a type I venous-venous shunt were allocated to the CHIVA arm, which is absolutely correct for "one-time surgery", while in the other four RCTs[3,5-7] all types of venous-venous shunt were allocated to the CHIVA arm, including the most prevalent type III shunts, that were incorrectly treated by "one-time surgery". Coming to figures, altogether these last four RCTs[3,5-7] allocated to the CHIVA arm 344 participants, but Pares *et al.*[5] reported 97 type III shunts over 167 limbs (58%), and Gonzàles-Cañas *et al.*[7] reported 54 type III shunts over 75 limbs (72%). With regard to Iborra-Ortega et al,[3] in their RCT there is no explicit mention of the type of venous-venous shunt. Further, with regard to Wang *et al.*,[6] in their RCT they used an unusual, too much simplified classification of venous-venous shunts which does not allow to make any comparison with the worldwide adopted classification of venous-venous shunts suggested by Franceschi,[13] used in the RCTs published by Carandina *et al.*, [4] Pares *et al.*, [5] and Gonzàles-Cañas *et al.*[7] However, for the RCTs published by Iborra-Ortega *et al.*[3] and by Wang *et al.*[6] we can reasonably assume that, given the natural prevalence of type III shunts,[13] they should have been at least 55-60%, corresponding to 27-30 limbs for each of the two RCTs. Summing up the type III shunt allocated to the CHIVA arm and incorrectly treated by "one-time surgery" in the four RCTs, we obtain that more than 200 of the 344 participants allocated to the CHIVA arm actually received procedures other than the CHIVA Cure, as the CHIVA strategy was not correctly applied, and, consequently, should not have been considered in the calculations reported in the last CR.[9] Finally, with regard to the RCT conducted by Gonzàles-Cañas *et al.*,[7] authors reported 11 clinical recurrences in the CHIVA arm. However, all the 11 clinical recurrences reported in the CHIVA arm were instrumentally detected at SFJ level and were, very likely, due to blunders

in the CHIVA tactic, as in the methods section there is no mention either of the metallic clip positioning or of the closure of the *fossa ovalis* with a non-absorbable suture. Further, with regard to the other 24 instrumental recurrences reported by Gonzàles-Cañas *et al.*,[7] those defined as "incompetent GSV without a drainage perforator", are the expected consequence of incorrectly treating the type III venous-venous shunt with the "one-time surgery".

Thus, it is reasonable to wonder how can the last CR on the CHIVA Cure[9] provide reliable conclusions if more than 200 over 419 participants allocated to the CHIVA arm actually received treatments other than the CHIVA Cure, due to incorrect CHIVA strategy and, sometimes, even to incorrect CHIVA tactic. Moreover, the authors divided the RCTs into two subgroups, "drained CHIVA"[4-6] and "non-drained CHIVA",[3,7,] but the criteria for including the RCTs in the former or in the latter subgroup are not clearly specified. Thus, again, it is reasonable wondering why, for instance, the 97 type III shunts treated by Pares[5] by one-time surgery have been classed in the subgroup "drained CHIVA", while the 54 type III shunts, equally treated by Gonzàles-Cañas[7] by one-time surgery, have been classed in the subgroup "non-drained CHIVA. Finally, it is also reasonable wondering why the last CR[9] has included two more RCTs[6,7] in the awareness that both RCTs, along with sharing the (unavoidable) high risk of "detection" and "performance" biases, as all the RCTs comparing the treatments for superficial venous insufficiency, were also at high risk of the (avoidable) "reporting" bias and showed a relevantly shorter follow-up, which led the authors to downgrade the grade of evidence from "moderate-certainty" to "low-certainty".

Coming to the recently released GLs from the European Society for Vascular Surgery,[17] the Recommendation 28, based on the results of six RCTs,[18-23] states: "For patients with great saphenous vein incompetence requiring treatment, endovenous thermal ablation is recommended as first choice treatment, in preference to high ligation/stripping and ultrasound guided foam sclerotherapy". Further, the Recommendation 35, based on the results of three RCTs,[20,21,24] states: "For patients with great saphenous vein incompetence requiring treatment, high ligation/stripping should be considered, if endovenous thermal ablation options are not available". Here, it is reasonable wondering how can the authors state that "endovenous thermal ablation is recommended as a first choice treatment" (Rec. 28) and that "high ligation/stripping should be considered, if endovenous thermal ablation options are not available" (Rec. 35) if none of the RCTs cited to support their recommendations included the CHIVA Cure. Finally, Recommendation 51, based on the last CR,[9] states: "For patients with superficial venous incompetence requiring treatment, ambulatory conservative hemodynamic treatment (CHIVA) may be considered, if performed by physicians experienced in this treatment strategy". This

seems to suggest that surgeons unexperienced in the CHIVA Cure, instead of training in the subject, should straight perform a destructive procedure, in spite of the worse results in terms of recurrences and post-surgical complications documented by Milone *et al*.[25] after stripping when compared to the results after CHIVA, achieved by surgeons experienced in both procedures. Further, the Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum[26] states: "CHIVA is a complex approach, and a high level of training and experience is needed to attain the results presented in the RCTs.[4,5,27] However, the results achieved by a few outstanding interventionists do not support offering this procedure to all practitioners. Although CHIVA has called attention to the importance of directing surgical procedures toward the patient's venous anatomy and function, it still requires considerable education of venous interventionists willing to learn this approach". Again, it is reasonable to wonder whether this contradicts what is expected of a specialist, *i.e.*, mastery of the treatment of diseases in his or her specialty, and to which extent this complies with the prescriptions of the European Charter of Patients' Rights.

A relevant ethical issue, which definitely does not comply with the prescriptions of the European Charter of Patients' Rights, also arises from the fact that, to the best of our knowledge, in the informed consent forms to be signed before undergoing destructive procedures there is no mention that the procedure will fatally deprive the patient of the GSV. RCTs include items such as complications, recurrences, and quality of life, but, surprisingly, neglect the chance of venous bypass related to the preservation of the GSV. Yet, this vital aspect of treating a benign disease should be considered in RCTs, for scientific reasons, and in informed consent forms, for ethical and even legal reasons. Thus, the systematic preservation of this graft by the CHIVA Cure should be considered in RCTs, CRs, and GLs.[28, 29] Autologous GSV is, in fact, the first-choice infra-inguinal graft,[30,31] as a valid alternative to angioplasty/stenting,[32] to treat the severe peripheral artery disease that may occur with advancing age and to ward off the severely disabling condition resulting from limb loss. Indeed, several studies have shown that spared GSVs after the CHIVA Cure can be successfully used as grafts because the dramatic decrease in the reflux flow resulting from the CHIVA Cure reduces the Trans-Mural Pressure (TMP) which, in turn, decrease the GSV caliber[33] and "maintains" the normal histologic architecture of the venous wall.[34] Further, once the oscillatory component of the reflux had been suppressed, Zamboni *et al.*[35] have shown a favorable modulation of the inflammatory endothelial phenotype that mitigates the inflammatory process responsible for the sustained damaging of venous valves and walls. Finally, the retrograde flow detected within the GSV after the CHIVA Cure does not represent a limitation to its use as a graft,[36,37] nor the presence of GSV bulges, which

are rare and can be "repaired",[36] nor the GSV fragmentation, which is seldom necessary in clinical practice (in authors' experience less than 2% of cases over more than 3,000 operated GSVs).

In conclusion, undoubtedly the CRs should meticulously assess all possible methodological biases[12] shown by the RCTs, in line with the long-standing and wide-world acknowledged tradition of the Cochrane Collaboration. However, some biases like the "detection" and the "performance" bias, that can be avoided in most RCTs, for instance, in those comparing the efficacy of drugs, are, unluckily, unavoidable in the RCTs comparing the treatments for SVI, and this, obviously, jeopardizes the grade of evidence derived from these RCTs.

Interestingly, Balshem *et al*.[38] have highlighted "the explicit separation of the process for assessing the grade of a body of evidence from the process for making recommendations based, "*in part"*, on those assessments. Although, intuitively, a higher grade of evidence is more likely to be associated with strong recommendations than a lower grade of evidence, a particular level of the grade of evidence does not imply a particular strength of recommendation. Sometimes, low or very low grade of the evidence can lead to a strong recommendation".[38] Further, Andrews *et al.*[39] have better clarified the words *"*in part*"*, stated by Balshem *et al*.,[38] whose meaning is that the grade of evidence is not the only factor affecting the recommendations. In fact, a careful assessment of the balance between desirable outcomes (typically, increased longevity, reduction in morbid events the intervention is designed to prevent, resolution of symptoms, improved quality of life, decreased use of resources) and undesirable outcomes (typically, decreased longevity, immediate serious complications, short-term relatively minor side effects, long-term rare serious adverse events, impaired quality of life, inconvenience/hassle, increased use of resources) is a key factor in determining the direction of recommendations.[39]

With regard to the CHIVA Cure, the RCTs published by Carandina *et al.*[4] and by Pares *et al*.,[5] this last in spite of the incorrect CHIVA strategy applied, have shown significantly better results in the CHIVA arm, in terms of both clinical and instrumental recurrences. Further, Guo *et al.*[40] in their "network" metanalysis, have compared the results from five treatments for superficial venous insufficiency (endovascular ablation, CHIVA Cure, sclerotherapy, high ligation, and stripping) and from four additional combination of the above treatments, in 39 RCTs, with overall 6,917 limbs, with a follow-up ranging from one to ten years. The focus was on long-term efficacy of the different procedures by assessing objective data, such as the Successful Treatment Rate (STR), defined as anatomic and functional completeness, with completely ablated, occluded, or stripped GSVs, by ultrasound confirmation, and clinical Recurrence Rate

(RR), assessed according to the Hobbs' classification.[10] Authors found that the CHIVA Cure was associated with the highest Odds Ratio of STR and with the lowest Odds Ratio of RR, when compared to the other procedures, so that the authors concluded: "Despite the existence of several limitations, the final conclusions showed that the long-term efficacy of CHIVA was superior to the efficacy of other procedures. The efficacy of this approach was based on a better physiological process, and this revolutionary approach should be widely applied in clinics".[40] Thus, at least with regard to the RCTs on the treatment for SVI that, unavoidably, are at high risk of methodological biases,[12] we should consider that even if RCTs show a "moderate-" or "low-certainty" grade of evidence, this does not mean at all that the treatment providing better results cannot represent a "strong in favor" recommendation, as quality of the evidence and strength of recommendations are, definitely, quite different concepts, as highlighted by the GRADE Working Group (Grades of Recommendation, Assessment, Development, and Evaluation).[38, 39] Further, with regard to the CHIVA Cure, CRs Authors should also exclude from calculations those cases that show technical blunders in the CHIVA strategy and/or in the CHIVA tactic.

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