



Automated advanced imaging in acute ischemic stroke. Certainties and uncertainties

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HIGHLIGHTS

- Advanced imaging are currently considered the method of choice for the selection of patients with acute ischemic stroke suitable for endovascular treatment in the late time window.
- Automated software packages are increasing being adopted for the calculation of the optimal selection parameters provided by advanced imaging which are collectively called target mismatch.
- Automated software platform have several limitations since are not interchangeable e can under- and overestimated infarct core volume.
- Selection remains suboptimal due to high rates of futile recanalization and restricted selection criteria resulting in a overselection.
- The routine use of advanced imaging for the selection of patients treated with endovascular therapy is still controversial due to some evidence that conventional imaging are not inferior to advanced imaging in establishing patients who can benefit from endovascular treatment.
- The combination of results coming from both conventional and advanced imaging could be the solution for improving our selection criteria.

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ABSTRACT

The purpose of this study was to review pearls and pitfalls of advanced imaging, such as computed tomography perfusion and diffusion-weighted imaging and perfusion-weighted imaging in the selection of acute ischemic stroke (AIS) patients suitable for endovascular treatment (EVT) in the late time window (6–24 h from symptom onset). Advanced imaging can quantify infarct core and ischemic penumbra using specific threshold values and provides optimal selection parameters, collectively called target mismatch. More precisely, target mismatch criteria consist of core volume and/or penumbra volume and mismatch ratio (the ratio between total hypoperfusion and core volumes) with precise cut-off values. The parameters of target mismatch are automatically calculated with dedicated software packages that allow a quick and standardized interpretation of advanced imaging. However, this approach has several limitations leading to a misclassification of core and penumbra volumes. In fact, automatic software platforms are affected by technical artifacts and are not interchangeable due to a remarkable vendor-dependent variability, resulting in different estimate of target mismatch parameters. In addition, advanced imaging is not completely accurate in detecting infarct core, that can be under- or overestimated. Finally, the selection of candidates for EVT remains currently suboptimal due to the high rates of futile reperfusion and overselection caused by the use of very stringent inclusion criteria. For these reasons, some investigators recently proposed to replace advanced with conventional imaging in the selection for EVT, after the demonstration that non-contrast CT ASPECTS and computed tomography angiography collateral evaluation are not inferior to advanced images in predicting outcome in AIS patients treated with EVT. However, other authors

Abbreviations: AIS, acute ischemic stroke; ASPECTS, Alberta Stroke Program Early CT Score; CBF, cerebral blood flow; CBV, cerebral blood volume; CTA, computed tomography angiography; CTP, computed tomography perfusion; DWI, diffusion-weighted imaging; EVT, endovascular treatment; IVT, intravenous thrombolysis; MRI, magnetic resonance imaging; MTT, mean transit time; NCCT, non-contrast CT; NIHSS, National Institute of Health Stroke Scale; PWI, perfusion-weighted imaging; RCTs, randomized controlled trials; Tmax, time to the peak of the residual function.

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confirmed that CTP and PWI/DWI postprocessed images are superior to conventional imaging in establishing the eligibility of patients for EVT. Therefore, the routine application of automatic assessment of advanced imaging remains a matter of debate. Recent findings suggest that the combination of conventional and advanced imaging might improving our selection criteria.

1. Introduction

Intravenous thrombolysis (IVT) and endovascular treatment (EVT) are the currently available reperfusion therapies for patients with acute ischemic stroke (AIS) that represents one of the leading causes of long-term disability and mortality worldwide [1,2]. It is well-known that the target of IVT and EVT is the rescue of ischemic penumbra, the reversibly damaged brain tissue at risk for infarction, located around the irreversibly injured infarct core [3]. More precisely, while infarct core is no longer viable, always evolving towards infarct because of cytotoxic edema resulting in cellular swelling and death, ischemic penumbra is a still viable tissue due to the activation of hemodynamic and metabolic compensatory mechanisms, such as leptomeningeal collaterals opening, cerebral autoregulation and increase in cellular oxygen extraction fraction [3–5]. However, in absence of reperfusion, compensatory responses gradually exhaust, and penumbra progressively transforms into infarction [4,6]. Therefore, ischemic penumbra is a potentially salvageable tissue if circulation is restored [1–5], typically surviving up to 24–48 h after symptom onset [7,8]. Based on these observations, an appropriate delineation of infarct core and ischemic penumbra regions is crucial for identifying patients who can benefit from reperfusion therapies as patients with small core and large penumbra are probably more likely to achieve a good outcome [9]. Precise quantification of core and penumbra is difficult with conventional imaging such as non-contrast CT (NCCT) and Computed Tomography Angiography (CTA). NCCT recognizes early ischemic changes (areas of weak parenchymal hypoattenuation such as focal hypodensity, obscuration of lentiform nucleus, loss of gray-white matter differentiation, loss of insular ribbon) corresponding to the infarct core and estimates their extent using the semiquantitative Alberta Stroke Program Early CT Score (ASPECTS) methodology but does not detect the ischemic penumbra [10]. CTA identifies the occlusion site and provides a detailed evaluation of collateral supply using two different techniques, single-phase CTA (sCTA) and multi-phase CTA (mCTA) but does not provide information about infarct core and ischemic penumbra [11]. Conversely, a recent randomized controlled trials (RCTs) showed benefit from reperfusion therapies in the late time window using advanced imaging [9]. In particular, the measurement of core and penumbra volumes with computed tomography perfusion (CTP) or magnetic resonance imaging (MRI) techniques, such as diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI), were proven to be a powerful tool for establishing the eligibility of AIS patients for IVT between 4.5 and 9 h and for EVT between 6 and 24 h after onset [9,12,13]. Of note, the calculation of core and penumbra volumes in these extended time window RCTs was performed with dedicated automatic software programs using prespecified thresholds [3,5,9]. Therefore, the ability to automatically elaborate CTP or PWI and DWI imaging seems crucial step to overcome the lack of standardization that is one of the most important limitations of advanced imaging [14,15]. Consequently, automated processing of advanced imaging is currently considered an essential requirement for the selection of AIS patients suitable for reperfusion therapies in the late time window [16,17]. However, as the routine application of automatic assessment of advanced imaging for the selection of patients with AIS candidates for reperfusion therapies remains controversial, and a detailed analysis on advantages and disadvantages of this approach is warranted to understand its value in clinical practice.

2. Automated selection with target mismatch

2.1. The mismatch concept

It is largely accepted that MRI is able to distinguish irreversibly and reversibly damaged brain tissue within the ischemic area. Cytotoxic edema characterizing infarct core is indicated by DWI lesion range, PWI lesion size corresponds to the total critically hypoperfused ischemic area infarcted and penumbral tissue is the difference between these two volumes, the so-called PWI-DWI mismatch, indicates ischemic penumbra volume (Fig. 1) [2,5,16,18,19]. However, the use of specific thresholds is needed for a correct delineation of the limits of infarct core and ischemic penumbra. Currently, critically hypoperfused tissue is recognized by time to the peak of the residual function absolute values greater than 6 s ($T_{max} > 6$ s) on PWI [20], whereas Apparent Diffusion Coefficient absolute values lower than $620 \times 10^{-6} \text{ mm}^2/\text{seconds}$ ($ADC < 620 \times 10^{-6} \text{ mm}^2/\text{s}$) represent infarct core [21]. On the other hand, for many years the difference between CTP abnormalities observed on mean transit time (MTT) and cerebral blood volume (CBV) maps was considered the best method for identifying salvageable brain tissues [22]. This model, named MTT-CBV mismatch, was based on the assumption that MTT defect size referred to total hypoperfused area and CBV defect extent described infarct core (in CBV maps ischemic penumbra is not visible due to normal or increased CBV levels resulting from the opening of collaterals) (Fig. 2) [23]. Relative MTT greater than 145 % of the contralateral normal side ($rMTT > 145\%$) and CBV absolute values lower than 2 mL/100gr ($CBV < 2 \text{ mL}/100\text{gr}$) were found to be the optimal cut-off values for detecting critical hypoperfused and infarcted regions, respectively [24]. Several studies reported high accuracy of CBV and MTT maps for determining infarct core and ischemic penumbra sizes [24–32] and a strong association between CTP MTT-CBV mismatch and functional outcome [26,30,33–36]. Nevertheless, other publications showed that the predictive value of CBV and MTT maps for the definition of infarcted and penumbral tissues was low [37–42]. In addition, many investigators demonstrated that the borders of infarct core and total hypoperfusion were more precisely estimated by CTP focal disturbances observed on cerebral blood flow (CBF) and T_{max} maps rather than on CBV and MTT maps, suggesting that T_{max} lesion extent minus CBF lesion size indicated ischemic penumbra (Fig. 3) [43–48]. This paradigm was termed T_{max} -CBF mismatch in which the best cut-off values for delineating critical hypoperfused and infarcted areas were established to be T_{max} values > 6 s and relative CBF threshold values less than 30 % of normally perfused tissue ($rCBF < 30\%$), respectively [9,12,16,17]. The superiority of T_{max} -CBF paradigm compared to MTT-CBV model in identifying infarct core and ischemic penumbra explains why T_{max} -CBF mismatch is now considered the method of choice and therefore was used for the selection of AIS patients candidates for reperfusion therapies in all MRI and CTP-guided RCTs recently published [12,49–51].

2.2. Optimal parameters for the selection: the target mismatch

The identification of optimal MRI and CTP parameters to identify AIS patients who could benefit from reperfusion therapies was considered as an essential condition for the selection of subjects suitable for IVT and EVT. Consequently, according to DEFUSE 2 (The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2) [52], in MRI and CTP-based RCTs patients were selected for therapy if they satisfied a combination of criteria derived from PWI-DWI or T_{max} -CBF mismatch

that was called target mismatch [16,49,51]. Therefore, patients meeting target mismatch criteria were judged having a favorable MRI or CTP profile with a small core and a large penumbra (Fig. 5) [16,48]. However, the parameters of target mismatch differed in RCTs based on advanced imaging (Table 1), such as EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial) [53] and SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment) [54] performed in the early time window for EVT within 6 h from symptom onset, DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) [55] and DAWN (Triage of Wake-up and Late Presenting Strokes Undergoing Neurointervention With Trevo) carried out in the late time window for EVT between 6 and 24 h after ictus [56] and EXTEND (Extending the Time for Thrombolysis in Emergency Neurological Deficits) realized in the late time window for IVT at 4.5–9 h after stroke [57]. More precisely, EXTEND-IA trial demonstrated the efficacy of combined EVT and IVT compared to IVT alone in patients selected within 4.5 h from symptom onset with a target mismatch including CTP parameters: infarct core volume < 70 mL, ischemic penumbra volume > 10 mL and mismatch ratio (the quotient between total hypoperfusion and core volumes) > 1.2. In SWIFT PRIME trial patients undergoing combined EVT and IVT within 6 h after stroke achieved more frequently a good outcome than controls treated with IVT alone after selection with a target mismatch characterized by MRI or CTP criteria: infarct core volume ≤ 50 mL, ischemic penumbra volume ≥ 15 mL and mismatch ratio > 1.8. DEFUSE 3 trial showed the association with favorable outcome in patients receiving EVT at 6–16 h after onset compared to controls treated with standard care, using as selection criteria a target mismatch consisting of MRI or CTP measures: infarct core volume < 70 mL, ischemic penumbra volume > 15 mL and mismatch ratio > 1.8. In DAWN trial patients treated with EVT at 6–24 h after stroke had better outcome compared to controls treated with standard care after selection with a target mismatch based on the mismatch between stroke severity and infarct core volume adjusted by age according to the following criteria: ≥ 80 years, National Institute of Health Stroke Scale (NIHSS) ≥ 10, core volume < 21 mL; < 80 years, NIHSS ≥ 10, core volume < 31 mL; < 80 years, NIHSS ≥ 20; core volume < 31–51 mL. EXTEND proved the effectiveness of IVT compared to placebo in patients selected at 4.5–9 h from onset with a target mismatch including MRI or CTP parameters: infarct core volume < 70 mL, ischemic penumbra volume > 10 mL and mismatch

ratio > 1.2. Among these RCTs guided by advanced imaging, only DEFUSE 3 and DAWN criteria were included in the American Heart Association/American Stroke Association (AHA/ASA) guidelines [58, 59]. EXTEND-IA and SWIFT PRIME were excluded because other concomitant RCTs demonstrated the benefit of EVT in the early time window (0–6 h) using conventional imaging. Although confirmed by a following meta-analysis [60], EXTEND criteria for IVT in extended time window (4.5–9 h) were not recommended probably because AHA/ASA guidelines were prepared before the publication of this trial. Thus, the use of advanced imaging is currently advocated only in the late time window (6–24 h) for EVT according to the target mismatch of DEFUSE 3 and DAWN. Of note, a recent study reported that DEFUSE 3 criteria were more inclusive than DAWN criteria as patients with pretreatment core infarct volume < 70 mL satisfying DEFUSE 3 criteria, but too large for inclusion according to DAWN criteria, demonstrated benefit from EVT [61]. In addition, another publication showed that DEFUSE 3 and DAWN criteria were equivalent for predicting outcome in patients receiving EVT at 6–24 h [62]. These findings suggest that the selection for EVT in the late time window could be based on DEFUSE 3 criteria only.

2.3. Automated processing of target mismatch

Although the optimal parameters of target mismatch varied across the different RCTs [53–57], they were always automatically calculated with the same dedicated software (RAPID; Rapid Processing of Perfusion and Diffusion; iSchemaView, Menlo Park, CA) that is at present considered a powerful tool to reduce imaging processing time and inter-operator variability, favoring reproducibility and rapid interpretation [63]. However, other available software platforms can provide the same performances represented by the automatic calculation of infarct core, total hypoperfusion and ischemic penumbra volume, as well as mismatch ratio. Some of these software packages use the same CTP thresholds for core (rCBF < 30%) and hypoperfused tissue (Tmax > 6 s) utilized by RAPID, such as Syngo.via CT Neuro Perfusion (Siemens Healthineers, Erlangen, Germany) [64] and Brainomix e-CTP (Brainomix Ltd., Oxford, UK) [65]. In contrast, other software programs identify irreversible and critically damaged tissue with different CTP cut-off values compared to RAPID, such as MISTar (Apollo Medical Imaging Technology, Melbourne, Australia) [66] and Olea Sphere (Olea Medical Solutions, La Ciotat, France) [67]. In particular, MISTar

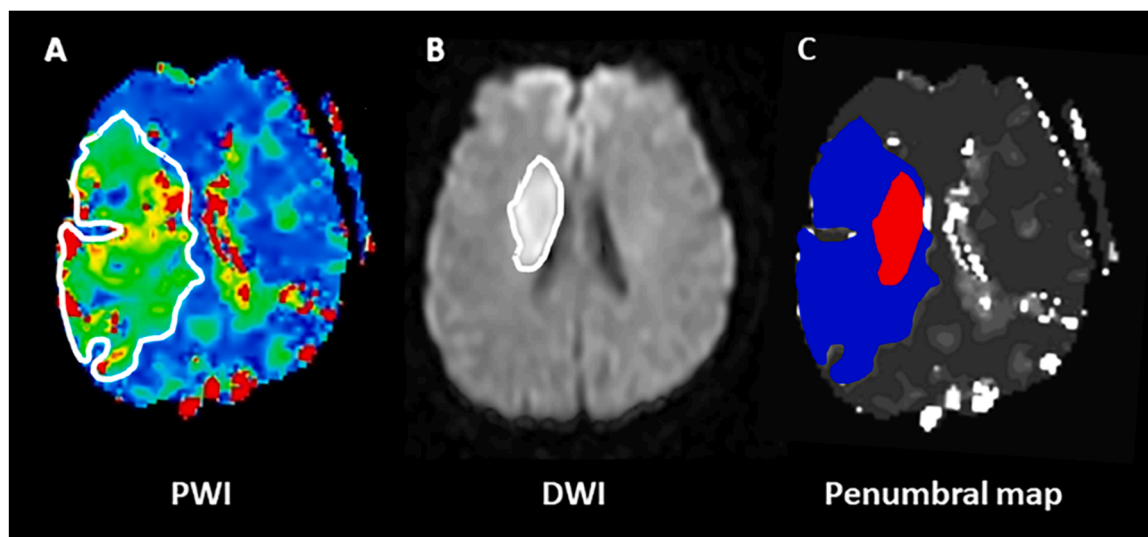


Fig. 1. The perfusion-weighted imaging (PWI)-diffusion-weighted imaging (DWI) mismatch in a 57 year-old patient with acute ischemic stroke (AIS) and ischemic lesion in the right middle cerebral artery (MCA) territory. *Panel A:* Color coded PWI time to the peak of the residual function (Tmax) map indicates total critically hypoperfused tissue; *Panel B:* DWI shows infarct core; *Panel C:* penumbral map illustrates infarcted tissue (red) and ischemic penumbra (blue) obtained from the difference between PWI and DWI lesion sizes.

determines total hypoperfusion extent with delay time (a map similar to Tmax) values more than 3 s (delay time > 3 s), whereas Olea Sphere defines infarct core size with rCBF values < 40 % (Fig. 4). Interestingly, Vitrea (Vital Images, Minnetonka, Minnesota) and Olea recently developed an algorithm alternative to deconvolution for generating CTP maps based on probabilistic Bayesian approach, obtaining different threshold values for core and penumbra compared to RAPID [68,69]. Vitrea Bayesian algorithm indicates total hypoperfusion with delay time values more than 5.7 s (delay time > 5.7 s) and infarct core with rCBF values < 38 %. Olea Bayesian algorithm defines total hypoperfusion with difference in time to peak compared with healthy brain more than 5 s (dTTP > 5 s) and infarct core with rCBF values < 25 %. The different algorithms and thresholds used by the various automatic software packages for recognizing core and penumbra regions are summarized in Table 2.

3. Automated selection in the real world

3.1. The selection remains suboptimal

The introduction of PWI-DWI mismatch on MRI and CTP Tmax-rCBF with automatic assessment of target mismatch parameters significantly improved the selection of AIS patients suitable for reperfusion therapies in the late time window for EVT and IVT [70]. Nevertheless, patient selection remains a challenge as around half of late-window patients do not achieve favorable outcome despite complete recanalization [71]. Furthermore, another important shortcoming affecting patient selection is the potential exclusion of some patients who could benefit from treatment due to the current restricted criteria [72]. This overselection was well described in two recent studies suggesting that the use of more permissive inclusion criteria could increase the number of patients treated with EVT in the late time window [73,74]. Lopez-Rivera and coworkers reported that the number of treatments with EVT in AIS patients with large vessel occlusion (LVO) admitted in both early and late time window was higher in centers with low advanced imaging utilization compared to those in which CTP was routinely used, without a significant increase in the incidence of poor outcome and hemorrhagic transformation [73]. More recently, Dittrich and colleagues showed that patients undergoing EVT at 6–24 h from onset and not satisfying

DEFUSE 3 and DAWN inclusion criteria had an elevated probability to achieve a favorable outcome, without a higher frequency of symptomatic hemorrhagic transformation, compared to controls treated with best medical therapy [74]. In the attempt to further extend the patient population receiving EVT in the late time window, the opportunity of treating patients with large core were extensively explored [75]. HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) meta-analysis [76] and preliminary studies [77,78] suggested the potential benefit of EVT in AIS patients with large core admitted in early and late time windows. Rates of symptomatic intracranial hemorrhage were increased compared to control group in HERMES analysis, but similar to controls in the other two studies. Large core was classified as a low Alberta Stroke Program Early CT Score (ASPECTS) of 0–4 by HERMES collaborators, a core volume > 100 mL assessed with CTP Tmax threshold values > 10 s by Nogueira et al. and a core volume > 50 mL evaluated with CTP rCBF cut-off values < 30 % by Rebello and associates. The effectiveness of EVT in patient with large core selected in early and late time windows was confirmed in subsequent publications using different definition of large core. Large core was considered as a core volume \geq 50 mL (rCBF < 30%) and/or a low ASPECTS < 5 in a secondary analysis of SELECT (Selection for Endovascular Treatment in Acute Ischemic Stroke) study [79], a core volume > 50 mL (rCBF < 30 % or ADC < 620×10^{-6} mm²/s) by Seners and coworkers [80], a low ASPECTS \leq 5 with a core volume > 70 mL (rCBF < 30%) by Bousslama et al. [81] and a core volume \geq 70 mL (rCBF < 30 %) by Garcia-Esperon et al. [82]. Interestingly, the last two investigations found that the association between EVT and good outcome was present only in patients with ASPECTS \leq 5 and a core volume \leq 70 mL [81] and those with a core volume 70–100 mL [82]. In addition, the benefit of EVT over controls, without an increased risk of intracerebral hemorrhage, was further highlighted by three meta-analyses in which large core was categorized as ASPECTS < 5 [83] and ASPECTS \leq 6 with a core volume \geq 50 mL [84,85]. Only one study was not consistent with these findings showing no association with a favorable outcome and an increased frequency of symptomatic hemorrhagic transformation in patients treated with EVT in the early time window with large core represented by ASPECTS < 5 [86]. More recently, three RCTs definitively demonstrated the usefulness of EVT in the late time window for AIS patients with large core who achieved

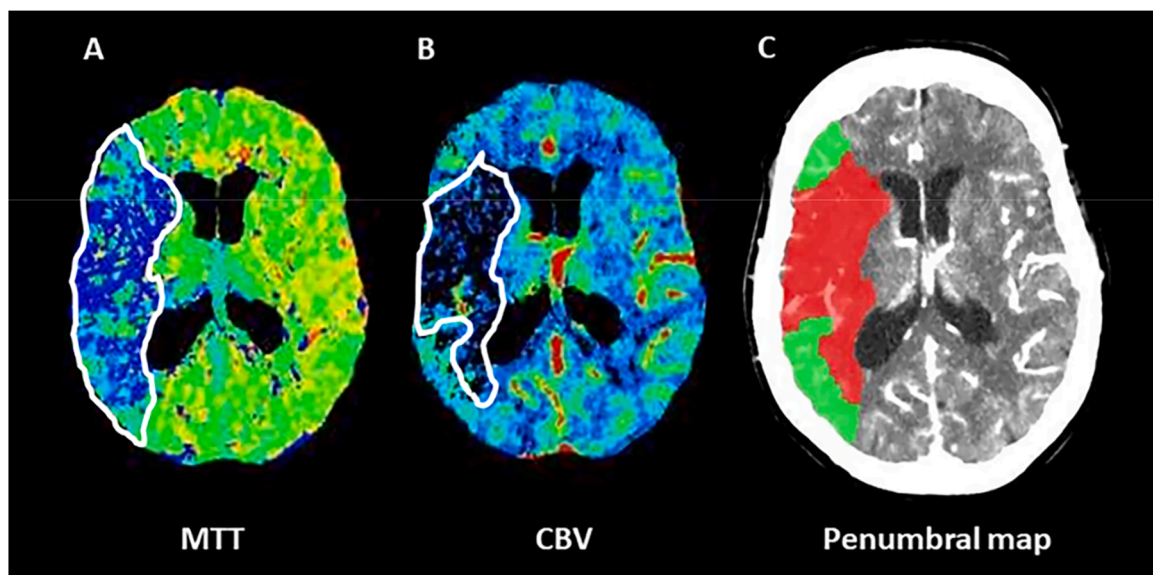


Fig. 2. The computed tomography perfusion (CTP) mean transit time (MTT)-cerebral blood volume (CBV) mismatch in a 65 year-old patient with acute ischemic stroke (AIS) and ischemic lesion in the right middle cerebral artery (MCA) territory. *Panel A:* Color coded MTT map indicates total critically hypoperfused tissue; *Panel B:* Color coded CBV shows infarct core; *Panel C:* penumbral map illustrates infarcted tissue (red) and ischemic penumbra (green) obtained from the difference between MTT and CBV lesion sizes.

higher odds of favorable outcome than controls treated with standard medical therapy and/or IVT [87–89]. Again, the definition of large core differed across these trials since SELECT-2 used a low ASPECTS 3–5 with a core volume ≥ 50 mL (rCBF $< 30\%$ or ADC $< 620 \times 10^{-6} \text{mm}^2/\text{s}$) [87], RESCUE-Japan LIMIT a low ASPECTS 3–5 [88] and ANGEL-ASPECT a low ASPECTS 3–5 with a core volume 70–100 mL (rCBF $< 30\%$ or ADC $< 620 \times 10^{-6} \text{mm}^2/\text{s}$) [89]. However, EVT for patients with extensive irreversible ischemic tissue damage remains challenging in clinical practice because of the lack of standardized methods for the definition of large core [75,90,91].

3.2. Accuracy of automatic software platforms

The increasing use of automatic software packages in the selection of patients suitable for EVT in the late time window focused the attention on the accuracy of these programs in correctly quantifying infarct core and ischemic penumbra volumes [92]. These investigations revealed that automated software programs had several limitations, resulting in postprocessing failure characterized by misclassification of core and penumbra volumes that occurred in about 11 % of cases [93]. First of all, automated advanced imaging outputs was disturbed by technical drawbacks, such as patient motion, poor contrast bolus due to delayed arrival or insufficient administration and too short acquisition leading to a truncation of perfusion curves [92,94,95]. On the other hand, the quality of postprocessed images was also reduced by imaging artifacts, such as the appearance of artifactual hypoperfused areas at the level of the skull base, posterior fossa and orbits, inducing errors in the calculation of perfusion abnormalities with overestimation of penumbra volume [94,95]. Although these artifactual perfusion lesions were easily identified by the operators [96], their removal implicates a manual segmentation that is not available in the currently used software platforms [94]. Nevertheless, despite these limitations and the demonstration that visual assessment of perfusion maps could be not inferior to automated estimation in defining infarct core and ischemic penumbra extent [97–99], the quantitative analysis offered by automatic softwares remained more reliable than a qualitative approach [96,100,101]. Another important flaw affecting the automated processing of penumbral maps was the demonstration that the different software packages were not interchangeable. In fact, when the performance of the various other software solutions was compared with RAPID, significant variability across vendors was found [94,95]. In particular, Syngo.via estimated larger or smaller infarct core, ischemic penumbra and final infarct

Table 1
Different parameters of target mismatch in the various RCTs based on advanced imaging.

RCT	Year of publication	Time window	Treatment	Target mismatch
EXTEND-IA	2015	≤ 4.5 h	EVT+ IVT vs IVT	core volume < 70 mL ischemic penumbra volume > 10 mL mismatch ratio > 1.2
SWIFT PRIME	2015	≤ 6 h	EVT+ IVT vs IVT	core volume ≤ 50 mL ischemic penumbra volume ≥ 15 mL mismatch ratio > 1.8
DEFUSE 3	2018	6–16 h	EVT vs BMT	core volume < 70 mL ischemic penumbra volume > 15 mL mismatch ratio > 1.8
DAWN	2018	6–24 h	EVT vs BMT	≥ 80 years, NIHSS ≥ 10 , core volume < 21 mL < 80 years, NIHSS ≥ 10 , core volume < 31 mL < 80 years, NIHSS ≥ 20 , core volume < 31 –51 mL
EXTEND	2019	4.5–9 h	IVT vs placebo	core volume < 70 mL ischemic penumbra volume > 10 mL mismatch ratio > 1.2

RTC = randomized controlled trial; EXTEND-IA = Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial; SWIFT PRIME = Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment; DEFUSE 3 = Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke; DAWN = Triage of Wake-up and Late Presenting Strokes Undergoing Neurointervention With Trevo; EXTEND = Extending the Time for Thrombolysis in Emergency Neurological Deficits; EVT = endovascular treatment; IVT = intravenous thrombolysis; BMT = best medical therapy; mismatch ratio = the quotient between total hypoperfusion and core volumes; NIHSS = National Institute of Health Stroke Scale

volumes compared to RAPID [102–105], although when the core thresholds were changed from rCBF $< 30\%$ to rCBF $< 20\%$ or smoothing was applied, Syngo.via results were more consistent with RAPID [106–109]. A good correlation was reported between RAPID and Brainomix for determination of core and penumbra volumes with Brainomix that, however, overestimated final infarct volume [65,104]. MISTar had a strong association with RAPID for estimation of core, penumbra and

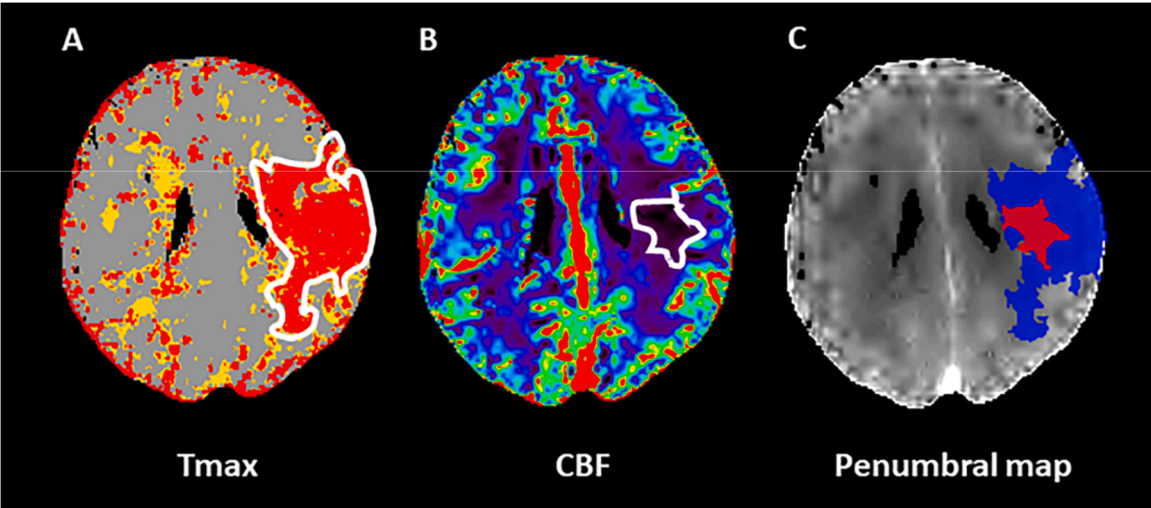


Fig. 3. The computed tomography perfusion (CTP) time to the peak of the residual function (Tmax)-cerebral blood flow (CBF) mismatch in a 69 year-old patient with acute ischemic stroke (AIS) and ischemic lesion in the left middle cerebral artery (MCA) territory. *Panel A:* Color coded Tmax map indicates total critically hypoperfused tissue; *Panel B:* Color coded CBF shows infarct core; *Panel C:* penumbral map illustrates infarcted tissue (red) and ischemic penumbra (blue) obtained from the difference between Tmax and CBF lesion sizes.

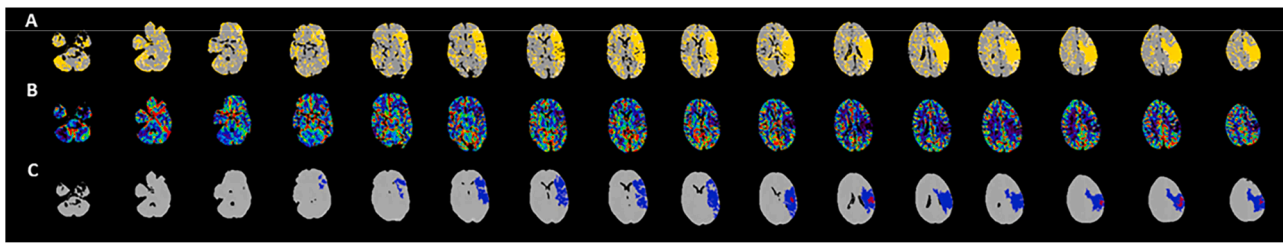


Fig. 4. Automatic calculation of target mismatch obtained with Olea Sphere from computed tomography perfusion in a 72 year-old patient with acute ischemic stroke (AIS) having an ischemic lesion in the left middle cerebral artery (MCA) territory. The patient was admitted at 13 h from onset with National Institute of Health Stroke Scale of 8, 6.57 mL of core volume, 94.75 mL of penumbra volume and 15.4 of mismatch ratio. Therefore, this patient satisfied both DEFUSE 3 and DAWN criteria. *Panel A:* Color coded time to the peak of the residual function (Tmax) maps indicate total critically hypoperfused tissue; *Panel B:* Color coded CBF maps show infarct core; *Panel C:* penumbral maps illustrate infarcted tissue (red) and ischemic penumbra (blue) resulting from the difference between Tmax and relative CBF lesion sizes.

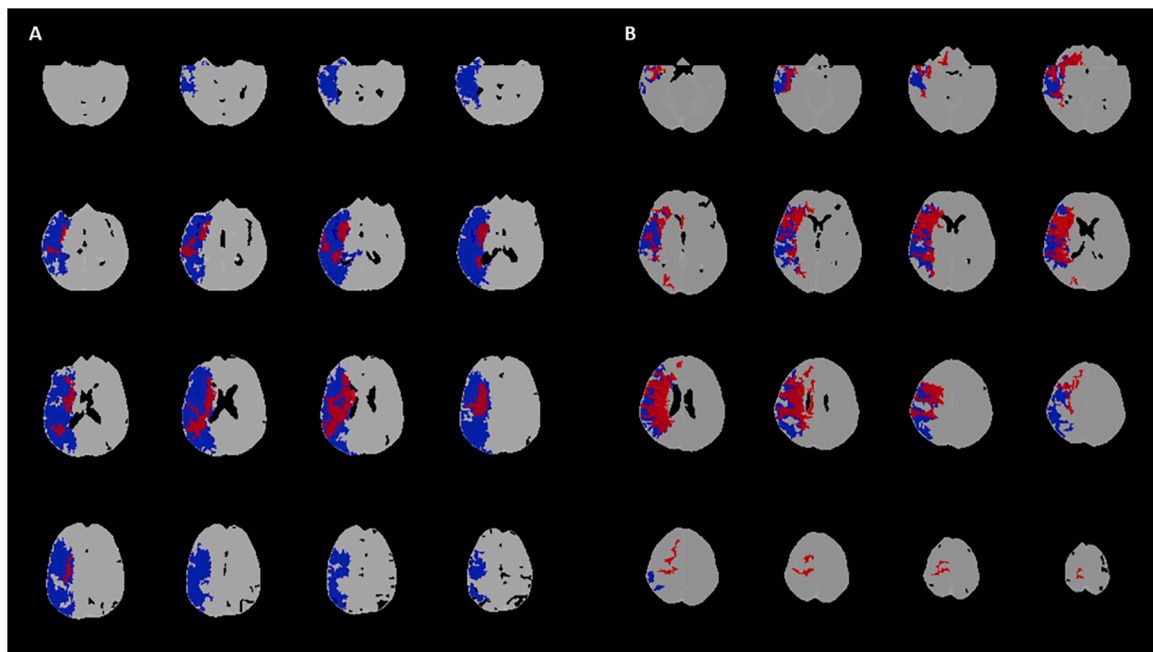


Fig. 5. Two illustrative examples of computed tomography perfusion favorable and unfavorable profiles obtained with automatic calculation of target mismatch (Olea Sphere). *Panel A:* a 68 year-old patient with acute ischemic stroke (AIS) having an ischemic lesion in the right middle cerebral artery (MCA) territory. The patient was admitted at 10 h from onset with National Institute of Health Stroke Scale of 20, 37.95 mL of core volume, 192.68 mL of penumbra volume and 5.1 of mismatch ratio. Therefore, this patient satisfied both DEFUSE 3 and DAWN criteria representing a typical DEFUSE 3/DAWN patient. *Panel B:* a 75 year-old patient with acute ischemic stroke (AIS) having an ischemic lesion in the right middle cerebral artery (MCA) territory. The patient was admitted at 15 h after onset with National Institute of Health Stroke Scale of 22, 82.30 mL of core volume, 9.81 mL of penumbra volume and 1.12 of mismatch ratio. Therefore, this patient did not satisfy both DEFUSE 3 and DAWN criteria representing a typical non-DEFUSE 3/non-DAWN patient.

final infarct volumes, but with a trend towards the overestimation of core [103,105,110,111]. Olea was less precise than RAPID in predicting core, penumbra and final infarct volumes due to its propensity to overestimate them [105,112,113]. In this context, the RAPID's accuracy for identifying core, penumbra and final infarct volumes was often moderate. Indeed, RAPID underestimated infarct core compared to the Bayesian algorithm used by Vitrea and Olea [68,114], whereas Vitrea was superior to RAPID and Olea in estimating penumbra [68,114] but inferior to Olea in predicting core volume [114]. Nevertheless, the main limitation of automatic software packages is probably the inaccuracy in detecting infarct core volume because of the lack of consensus on the optimal cut-off values [95,115]. The most pronounced effect of this weakness was the inability to obtain a reliable measurement of ischemic penumbra [92,115]. An additional reason that could explain the difficulty of automated postprocessed imaging in delineating infarct core was the evidence that DWI lesions can be reversible and CTP thresholds for infarct core were time-dependent [9,115]. Reversal of DWI lesions

consisted in the disappearance on follow-up images of DWI ischemic abnormalities visible at onset [116–120]. DWI reversibility was reported in a variable proportion ranging from 11 % to 50 % of cases in the early time window and ascribed to early recanalization. As demonstrated in prior Positron Emission Tomography studies [121–123], these findings suggest that DWI lesions not only reflect the cytotoxic edema of the tissue irreversibly destined to infarction, but also include a portion of ischemic penumbra [116]. Concerning CTP, it was clearly demonstrated that the optimal values for defining infarct core changed over time because the amount of tissue that infarcted increased with the increasing of CT-to-recanalization time [124,125], onset-to-imaging time [126] and onset-to-recanalization time [127–129]. Therefore, the time-dependence of CTP cut-off values for delineating infarct tissue implies that the identification of rigid CTP core thresholds can currently be considered unlikely [115] and might lead to underestimation or overestimation of infarct core size [94,95]. The suboptimal performance of automated computer-aided detection of infarct core volume accounts

Table 2
Different algorithms threshold values for automatically identifying infarct core and ischemic penumbra sizes.

Software	Algorithm	Thresholds for total hypoperfusion	Thresholds for infarct core
RAPID (iSchemaView)	Deconvolution	Tmax > 6 s	rCBF< 30%
SYNGO.VIA (Siemens Healthineers)	Deconvolution	Tmax > 6 s	rCBF< 30%
BRAINOMIX e-CTP (Brainomix)	Deconvolution	Tmax > 6 s	rCBF< 30%
MISTAR (Apollo Medical Imaging Technology)	Deconvolution	delay time > 3 s	rCBF< 30%
OLEA SPHERE (Olea Medical Solutions)	Deconvolution	Tmax > 6 s	rCBF< 40%
OLEA SPHERE (Olea Medical Solutions)	Bayesian	dTTP > 5 s	rCBF< 25%
VITREA (Vital Images)	Bayesian	delay time > 5.7 s	rCBF< 38%

Tmax = time to the peak of the residual function; rCBF = relative CBF of ischemic area compared to contralateral normal side; dTTP = difference in time to peak of ischemic area compared with healthy brain

for two important conditions that can be experienced in clinical practice: a CTP core underestimation referred as perfusion scotoma [130] and a CTP core overestimation termed ghost infarct [131]. The perfusion scotoma represents a mismatch between the presence of a visible hypodensity on NCCT and a smaller core volume on CTP at onset [130, 132,133]. This situation occurred in about 25 %– 36 % of cases in the early time window (<6 h from onset) and in about 20–25 % of patients in the late time window (>6 h after onset) and was attributed to a spontaneous reperfusion of infarcted tissue due to a good collateral status [130,133]. In this case, a possible solution could be the analysis of collaterals extent: the presence of a large core on NCCT, small core on CTP and good collaterals are highly suggestive of perfusion scotoma (Fig. 6). Conversely, the ghost infarct referred to the presence of a large infarct on pretreatment CTP with a smaller or absent final infarct volume on follow-up imaging [131,134–137]. The incidence of this phenomenon were higher in the early time window, where it ranged from 15 % (<6 h after onset) to 20 % (<4.5 h from onset) of subjects [131, 135–137], but can also occur in the late time window (>6 h after stroke) [134]. However, a pooled analysis including patients from HERMES and EXTEND-1A TNK (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke) datasets reported that an overestimation of

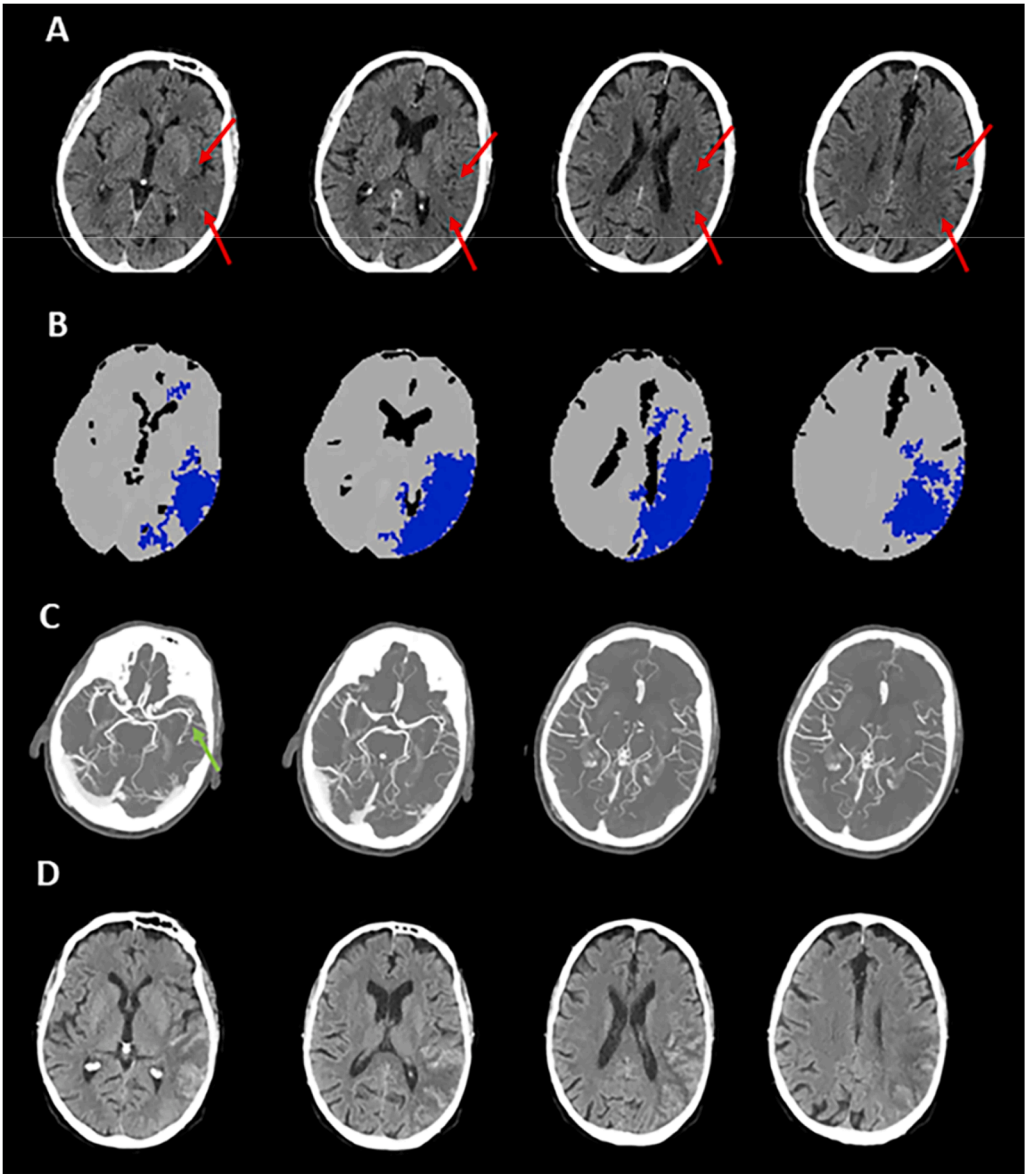


Fig. 6. An illustrative case of computed tomography perfusion (CTP) scotoma obtained with automatic calculation of target mismatch (Olea Sphere). A 59 year-old patient with acute ischemic stroke (AIS) having an ischemic lesion in the left middle cerebral artery (MCA) territory due to the occlusion of M2 segment admitted at 6 h after onset. A visible hypodensity on non-contrast computed tomography (NCCT) in ASPECTS regions I, M2, M3 M5 and M6 resulting in ASPECTS = 5 (Panel A), without detection of infarct core on CTP (Panel B), and with good collaterals on multiphase computed tomography angiography (Panel C). Follow-up NCCT performed at 24 h indicates a final infarct volume overlapping the hypo-attenuated NCCT lesion observed at admission with hemorrhagic transformation (Panel D).

infarct core by CTP was present only in 5 % of cases [138]. Poor collaterals were the major factor associated with ghost infarct (Fig. 7) [131, 137, 139], but large core volume at onset and short CT-to-recanalization time and onset-to-imaging time can favor the occurrence of ghost infarct [140]. Recent studies proposed a solution to overcome this issue, represented by the use of a more conservative rCBF threshold (<20 % instead of 30 %) that substantially reduced the number of patients with ghost infarct [141] and was mainly suitable to patients receiving EVT, but not to those treated with IVT [127]. Overall, the incorrect identification of core and penumbra sizes due to software limitations and vendor-dependent variability could justify the results emerged from a previous HERMES meta-analysis [141] and a recent study evaluating the accuracy of automated software programs in stroke diagnosis [142]. HERMES collaborators reported that patients with small infarct core volume achieved more frequently a good clinical outcome, without any significant association between infarct tissue size and the beneficial effect of EVT over controls [141]. Wardlaw and coworkers showed that the proportion of patients correctly diagnosed by automated software packages varied from 44 % to 83 % in case of ischemic patients and from 7 % to 43 % for subjects without ischemia (stroke mimics) [142].

4. Imaging modalities for the selection: Conventional versus advanced

4.1. Evidence that conventional imaging is enough for patients' selection

The potential suboptimal accuracy of advanced imaging prompted some investigators to explore the ability of conventional imaging to identify AIS patients with LVO who can benefit from EVT in the late time window. Bouslama et al. reported an identical association with clinical outcome for AIS patients treated with EVT after selection with NCCT ASPECTS ≥ 6 or advanced imaging according to DEFUSE 3 and DAWN criteria [143]. In addition, a publication from Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) registry found that the selection with favorable NCCT ASPECT profile combined to good collateral on sCTA did not result in a high proportion of poor outcome [144]. These findings were extended in a multicenter study showing no differences in functional outcome, incidence of hemorrhagic transformation and mortality between patients selected with NCCT ASPECTS ≥ 5 –7 and advanced imaging following DEFUSE 3 and DAWN criteria [145]. These results were confirmed by Porto and colleagues in a study from the Stroke Thrombectomy and Aneurysm Registry (STAR)

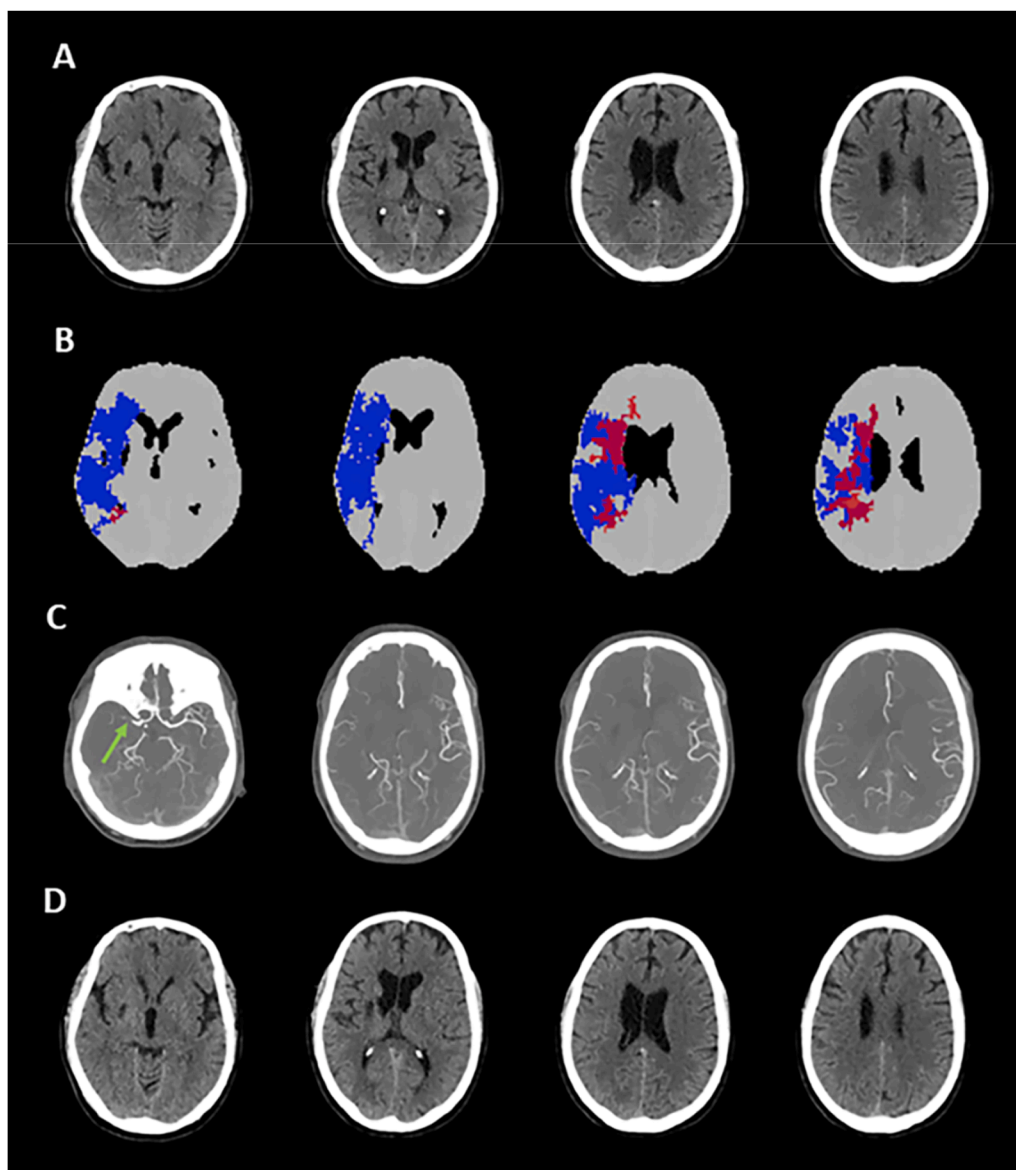


Fig. 7. An illustrative case of computed tomography perfusion (CTP) ghost infarct obtained with automatic calculation of target mismatch (Olea Sphere). A 63 year-old patient with acute ischemic stroke (AIS) having an ischemic lesion in the right middle cerebral artery (MCA) territory due to the occlusion of M1 segment admitted at 1.5 h after onset. The absence of hypodense lesion on non-contrast computed tomography (NCCT) with ASPECTS = 10 (Panel A), in presence of infarct core on CTP (Panel B), and with poor collaterals on multiphase computed tomography angiography (Panel C). Follow-up NCCT performed at 24 h did not indicate any final infarct volume (Panel D).

database [146]. The equivalence between NCCT ASPECTS and CTP criteria for patient's selection was also confirmed in the early time window [147–149]. Next, Bouslama and colleagues demonstrated that ischemic core volume automatically calculated with Brainomix software and CTP DEFUSE 3 target mismatch measured with RAPID were equivalent in predicting final infarct volume [150]. However, an editorial associated to this publication pointed out that automated evaluation of infarcted tissue with NCCT and CTP overestimated and underestimated final infarct volume, respectively, suggesting that the correct delineation of infarct core with imaging modalities remains a matter of debate [151]. On the other hand, the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial demonstrated the utility of collateral assessment with mCTA in the selection of AIS patients undergoing EVT within 12 h from onset as patients with good collaterals achieved more frequently a favorable outcome than controls treated with standard medical therapy [152]. Therefore, some authors tested the potential of mCTA as selection tool for patients treated with EVT in comparison to advanced imaging in the late time window. Kim et al. were the first to report that the incidence of favorable outcome was similar in patients who were considered eligible for EVT according to these criteria (good collaterals) or CTP DEFUSE 3 and DAWN target mismatch [153]. A similar effect on functional outcome was obtained in other three studies comparing patient selection with mCTA evaluation of collateral filling and CTP DAWN and/or DEFUSE 3 criteria [154,155]. Furthermore, combined NCCT ASPECTS and collateral-guided selection was comparable to CTP-guided selection in determining final infarct volume and clinical outcome in a pooled analysis of data coming from DAWN, DEFUSE-3 and ESCAPE-NA1 trials [156]. The predictive value for final infarct volume of mCTA collateral assessment and CTP-aided parameters did not differ in another publication as well [157]. Next, a pooled analysis from Selection of Late-window Stroke for Thrombectomy by Imaging Collateral Extent (SOLSTICE) Consortium established that the selection with sCTA or mCTA collateral score and with combined collateral and perfusion imaging led to similar functional outcome [158]. More important, the role of collateral grading in determining the eligibility of candidates for EVT in the late time window (6–24 h after onset) was more recently validated in MR CLEAN-LATE trial in which patients were selected for EVT if having visible collaterals on sCTA or mCTA and clinical outcome was better in subjects receiving EVT than in controls not treated with EVT [159]. Collectively, these findings were consistent with previous studies proving that predictive value of advanced imaging for final infarct volume, as well as penumbral salvage and infarct growth were collateral dependent. In fact, infarct core was smaller than predicted in presence of good collaterals and larger than predicted when collaterals were poor [160] and penumbral rescue and infarct expansion were associated with collateral extend and not with time [161,162]. In addition, there is cumulative evidence indicating that conventional imaging is not inferior to advanced imaging for identifying AIS patients suitable for EVT in the extended time window, suggesting that conventional imaging could replace advanced imaging for determining patient eligibility. This was the reason why some researchers recently proposed to adopt more simplified imaging selection criteria for these patients based on NCCT and CTA and not on MRI or CTP [163,164].

4.2. Evidence that advanced imaging is necessary for patients' selection

In contrast with the above-mentioned publications, other studies showed that advanced imaging remained superior to conventional imaging in the selection of AIS patients receiving EVT. Albers analyzed the recent RCTs and reported that the treatment effect was larger in the late than in early time windows, the so-called late window paradox, due to the use of advanced imaging with automatically calculated target mismatch in the extended time window [165]. Moreover, the treatment effect was greater also in the early time window when advanced imaging was used for the selection [165]. Consistent with this view, CT Perfusion

to Predict Response to Recanalization in Ischemic Stroke Project (CRISP) investigators [166] and an analysis of ESCAPE trial dataset [167] showed that a successful recanalization was associated with a good functional outcome in patients treated with EVT having a favorable CTP profile according to DEFUSE 3 criteria in both early and late time window. In addition, automatically calculated CTP ischemic core volume predicted clinical outcome better than NCCT ASPECTS within 18 h from onset [168], whereas a large penumbra extent assessed according to EXTEND criteria was a strong predictor of favorable outcome in the early time window [169]. Next, while infarct core volume and total hypoperfusion volumes, as measured by DEFUSE 3 criteria, predicted final infarct volume in the delayed time window with good accuracy [170], only a moderate correlation between NCCT ASPECTS and automatically estimated CTP infarct core volume was demonstrated at 6–24 after stroke [171]. A meta-analysis confirmed that the use of advanced imaging for EVT selection was associated with an improved functional outcome compared to conventional imaging in both early and late time window [172]. Furthermore, an association between pretreatment CTP EXTEND-IA, SWIFT PRIME, DEFUSE 3 and DAWN inclusion criteria and clinical outcome was a more recently found in the early time window (<6 h after onset), independent of time of onset [173]. Of note, a following study revealed that part of the hypodensity observed on NCCT did not represent infarct core, but ischemic penumbra, making it difficult to recognize irreversibly damaged tissue with this technique [174]. On the other hand, CTP-based selection criteria predicted clinical outcome better than mCTA classification of collaterals [175]. Finally, as reported in two studies, functional outcome of patients treated with EVT in both early and delayed time windows was not dependent from onset time, but rather correlated with salvageable penumbra volume that only advanced imaging can quantify [176,177]. Therefore, as some authors assumed that time of onset was not a sufficient reason to exclude patients from EVT, a change in the selection paradigm was proposed suggesting a switch from time-based to tissue or imaging-based models for defining patients who can be eligible for EVT [178–180].

4.3. An interpretation of current evidence

The conflicting results obtained by the above discussed studies might be explained by an accurate analysis of some pivotal publications. SELECT group conducted a study on patients successfully treated with EVT both in the early (0–6 h from onset) and extended (6–24 h after onset) windows [181]. A good outcome was achieved in 58 % of subjects with favorable NCCT ASPECTS (ASPECTS \geq 6) and favorable CTP (core volume<70 mL, ischemic penumbra volume>10 mL and mismatch ratio>1.2) profiles, in 46.4% of cases with unfavorable NCCT ASPECTS (ASPECTS<6) and favorable CTP patterns, 23.5 % of cases with favorable NCCT ASPECTS and unfavorable CTP patterns in and in 0 % of patients when both NCCT ASPECTS and CTP profiles were unfavorable. Ospel and associates observed a population of AIS patients receiving EVT within 12 h of symptom onset on behalf of The Precise and Rapid Assessment of Collaterals Multi-phase CTA in the Triage of Patients With Acute Ischemic Stroke for IA Therapy (Prove-IT) investigators [182]. Patients eligible for endovascular treatment by combined CTP (core volume<70 mL, ischemic penumbra volume>15 mL and mismatch ratio>1.8) and mCTA (good collaterals) criteria had favorable outcome in 62–87 % of cases, depending on CTP thresholds used for core definition (rCBF<30 %, CBF<7 mL/100 g/min or CBV<2 mL/100 g). mCTA eligibility criteria selected more patients (91 %) than CTP eligibility criteria (7–36 %), but with lower good outcome rates (53–57 %). A good outcome was found in 51–62 % patients who were not eligible by either mCTA or CTP criteria. Dhillon and coworkers reported an association between EVT and functional outcome in a large population of patients admitted in the late time window and selected only with NCCT ASPECTS and without advanced imaging [183]. However, the same group also showed that, always in a large cohort of AIS patients, the use of perfusion images improved functional independence compared to

conventional images in both early and delayed time windows, although CTP definition of core and penumbra was obtained with variable methods including automated evaluation and visual assessment [184]. This last observation was in line with some recent studies showing that the efficacy of EVT in the late time window was similar to RCTs when patients were selected with visual inspection of classical CTP MTT-CBV mismatch using an infarct core size $< 50\%$ of total hypoperfusion extent, approximately corresponding to a mismatch ratio > 1.8 , as alternative method for automatic calculation of core and penumbra [185,186]. Finally, in a more recent meta-analysis CTP-aided selection did not improve clinical outcome in patients undergoing EVT compared to NCCT selection in the extended time window, but it was associated with lower mortality [187]. Taken together, these findings suggest that the selection of patients suitable for EVT based on conventional imaging results in an inclusion of a larger population of AIS patients, but with lower rates of good outcome compared to selection guided by advanced imaging. In addition, these results indicate that higher rates of good outcome are achieved when conventional and advanced images are used in combination and confirm that our selection criteria are currently suboptimal.

5. Current views and future directions

The growing and controversial body of evidence accumulating in these last years on the selection of AIS patients for reperfusion therapies suggests that the eligibility criteria based on advanced imaging have limitations, but they can be currently still considered as the method of choice for identifying patients which can benefit from EVT. However, the selection can also be performed with conventional imaging alone obtaining the inclusion of a high number of patients but with an expected decreased incidence of favorable outcome. Another suggestion emerged from our analysis is that advanced imaging could be used to determine the eligibility of patients for EVT in the early time window. Anyway, the main take home message from the examined studies seems that a selection paradigm based on the integration between conventional and advanced images might lead to higher rates of good outcome. Nevertheless, selection criteria have to be improved as the number of futile recanalization remains too high. Following this direction, a recent study [188] explored the impact on outcomes of the previously published Tmax-Tmax mismatch [124] in patients admitted within 24 h and receiving EVT. In this model, in which core and penumbra were

identified using only one CTP map, critically hypoperfused tissue was indicated by Tmax with threshold value > 9.5 s, irreversibly injured tissue was delineated by Tmax with threshold value > 16 s and ischemic penumbra was defined by Tmax value > 9.5 s minus Tmax > 16 lesions (Fig. 8). All the volumes of these Tmax lesions were automatically calculated and strongly correlated with final infarct volume and functional independence at 3 months. In addition, a total hyperfusion volume ≤ 111.6 mL, a core volume ≤ 67.0 mL, a penumbra volume ≤ 58.3 mL and mismatch ratio > 2.5 were recognized as the optimal parameters predicting good outcome and then represented the Tmax target mismatch. However, these new criteria need to be validated in future studies demonstrating the non-inferiority or the superiority of Tmax target mismatch to DEFUSE 3 and DAWN criteria in the selection of patients suitable for EVT. Interestingly, two recent publications proposed a dedicated software that was able to automatically generate tissue maps directly from mCTA acquisition [189,190]. These mCTA-derived delay maps were very similar to Tmax maps and could be useful to reduce the radiation dose and acquisition time of CT protocol. On the other hand, the development of this technology could allow a more rapid and combined analysis of mCTA and CTP data. Therefore, further studies are justified to understand whether this novel approach based on Tmax maps with an integration between mCTA and Tmax findings can contribute to improve our ability to recognize AIS patients who can benefit from EVT. In this case, this novel paradigm could be incorporated in the CT workflow adopted in clinical practice.

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Morotti Andrea: Writing – review & editing, Writing – original draft, Supervision. **Fainardi Enrico:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Conceptualization. **Busto Giorgio:** Writing – review & editing, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

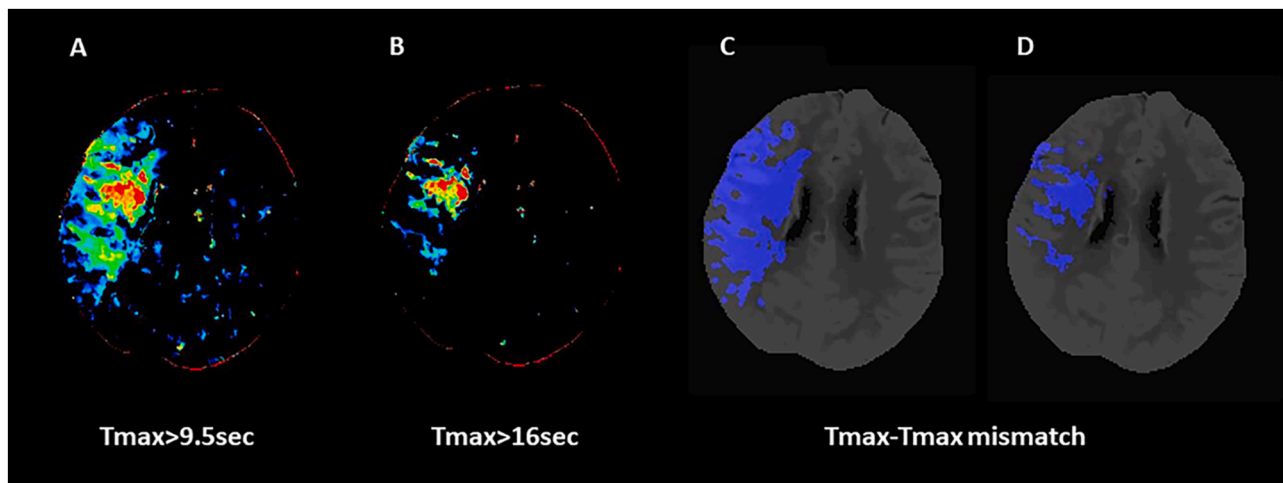


Fig. 8. The computed tomography perfusion (CTP) Tmax-Tmax mismatch in a 58 year-old patient with acute ischemic stroke (AIS) and ischemic lesion in the right middle cerebral artery (MCA) territory. *Panel A:* Color coded Tmax map with threshold value > 9.5 s indicates total critically hypoperfused tissue; *Panel B:* Color coded Tmax map with threshold value > 16 s shows infarct core; *Panel C:* Tmax > 9.5 s volume automatically segmented on CTP averaged images. *Panel D:* Tmax > 16 s volume automatically segmented on CTP averaged images. The difference between Tmax > 9.5 s and Tmax > 16 s volumes represents Tmax-Tmax mismatch. Tmax = time to the peak of the residual function.

the work reported in this paper.

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