

# An updated systematic review and meta-analysis on impedance threshold devices in patients undergoing cardiopulmonary resuscitation

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Heart, Lung and Vessels. 2014; 6(2): 105-113

## ABSTRACT

**Introduction:** Uncertainty persists on the clinical impact of impedance threshold devices in out-of-hospital cardiac arrest. We conducted an updated systematic review on impedance threshold devices.

**Methods:** Several databases were searched for studies testing the effectiveness of impedance threshold devices in patients with cardiac arrest. The primary endpoint was long-term survival.

**Results:** Seven trials (11,254 patients) were included. In 4 studies (2,284 patients) impedance threshold devices were used with active compression-decompression-cardiopulmonary resuscitation, and in the others alone. Overall, impedance threshold devices did not impact on the rate of return of spontaneous circulation (odds ratio = 1.17 [0.96-1.43],  $p = 0.114$ ), favorable neurologic outcome (odds ratio = 1.56 [0.97-2.50],  $p = 0.065$ ), or long-term survival (odds ratio = 1.22 [0.94-1.58],  $p = 0.127$ ). These analyses were fraught with heterogeneity (respectively,  $p = 0.055$ ,  $p = 0.236$ , and  $p = 0.011$ ) and inconsistency (respectively, I-squared = 51%, I-squared = 27%, and I-squared = 67%). Exploratory analysis showed that combined use of impedance threshold devices with active compression-decompression significantly increased the likelihood of return of spontaneous circulation (odds ratio = 1.19 [1.00-1.40],  $p = 0.045$ ), favorable neurologic outcome (odds ratio = 1.60 [1.14-2.25],  $p = 0.006$ ), and long-term survival (odds ratio = 1.52 [1.11-2.08],  $p = 0.009$ ). The favorable impact of the interaction between impedance threshold devices and active compression-decompression was also confirmed at meta-regression analysis (respectively,  $b = 0.195$  [0.004-0.387],  $p = 0.045$ ,  $b = 0.500$  [0.079-0.841],  $p = 0.018$ ,  $b = 0.413$  [0.063-0.764],  $p = 0.021$ ).

**Conclusions:** The evidence base on impedance threshold devices is apparently inconclusive, with a neutral impact on clinically relevant outcomes. However, exploratory analysis focusing on the combined use of impedance threshold devices with active compression-decompression suggests that this combo treatment may be useful to improve patient prognosis.

**Keywords:** active compression-decompression, cardiopulmonary resuscitation, impedance threshold device, return of spontaneous circulation.

## INTRODUCTION

Despite major improvements in prevention and management strategies, patients with out-of-hospital cardiac arrest (OOHCA) continue to face an ominous prognosis, especial-

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ly when focusing on the likelihood of long-term survival with satisfactory neurologic function (1, 2). Developments to improve the clinical outlook which have been recently introduced into mainstream practice include mechanical chest compression devices for cardiopulmonary resuscitation (CPR), therapeutic hypothermia, and extra-corporeal membrane oxygenation (ECMO) (2, 3). Another interesting yet simple technology designed to improve the results of CPR is the impedance threshold device (ITD) (4). It consists of a valve interconnected between the patient airways and the ventilation tools used during CPR (i.e. endotracheal tube, supraglottic airway, or face mask), and aims to decrease intrathoracic pressure during the release phase of CPR, thus increasing venous return to the heart, yet without impeding ventilation. Notably, it does so without impeding positive pressure ventilation or passive exhalation (5).

Experimental studies in animals and humans have suggested that it can increase both myocardial and cerebral perfusion, passively exploiting the forces generated during cardiac massage, especially when combined with an active compression-decompression-CPR (ACD-CPR) method (4, 6-8). Most recent data suggest that ITD could be beneficial even in conscious yet hypotensive patients, thus supporting its overall efficacy and safety profile (9).

However, clinical evidence on the impact of ITD for OOHCA remains heterogeneous. A prior meta-analysis published by our group in 2008 suggested that ITD could improve the likelihood of short- and mid-term favorable outcomes, but was limited by the small sample size (5 trials, 833 patients) (10). Most recently, two large studies have focused on the use of ITD in the management of patients with OOHCA undergoing CPR, with disappointingly conflicting results (11, 12). This is at odds with real-world observational data, which suggest

that ITD has a significant beneficial impact on patient prognosis (13, 14). As systematic reviews of randomized trials represent a unique opportunity to summarize and appraise the clinical evidence on any given issue (15-18), we aimed to conduct an updated and comprehensive systematic review and meta-analysis on ITD during CPR for OOHCA aiming to reconcile such differences and explore suitable moderators.

## METHODS

*Design.* This review was conducted in keeping with The Cochrane Collaboration recommendations and PRISMA guidelines (19, 20). All reviewing activities were performed independently by two experienced reviewers, with divergences resolved after consensus.

*Search.* Randomized trials were searched in MEDLINE/PubMed according to a strategy modified from Biondi-Zoccai et al. (21), using as key-words: cardiac arrest, impedance threshold device, and random\* trial\* (with \* denoting a wildcard). Additional searches were conducted in the Cochrane Library, Google Scholar, and Scopus. Searches were finally updated on March 20, 2014.

*Selection.* Citations were first screened at the title/abstract level, and retrieved as full articles if potentially pertinent. Studies were finally included if reporting on a randomized clinical trial focusing on ITD versus any control treatment in patients with OOHCA, excluding duplications.

*Abstraction and appraisal.* Relevant design, patient, procedural, and outcome details were extracted. Specifically, outcomes of interest were: return of spontaneous circulation (ROSC), favorable neurologic outcome (modified Rankin score  $\leq 3$ ), and survival at the longest available follow-up. Internal validity was appraised with established methods (19), detailed quantifying the risk of selection, performance, attrition

and selection bias. In addition, the risk of potential conflicts of interest was explicitly adjudicated.

*Analysis.* Continuous variables are described as means and categorical ones as counts or percentages. Meta-analysis was performed pooling odds ratios (OR), together with 95 % confidence intervals, with both fixed-effects and random-effects models. Statistical heterogeneity and inconsistency were appraised with chi-squared test and I-squared, respectively. In addition, the Egger’s linear regression test was used to appraise small study effects and meta-regression was performed preliminarily to identify potential effect modifiers (distinguishing two separate groups of studies

[ITD alone vs ITD plus ACD-CPR] with a dummy variable). Two-tailed statistical significance was set at the 0.05 level for hypothesis testing for effect, and at the 0.10 level for hypothesis testing for heterogeneity, with p values unadjusted for multiplicity reported throughout. Computations were performed with Comprehensive Meta-Analysis software (Biostat, Englewood, NJ, USA).

**RESULTS**

A total of 4,548 citations were screened (56 from The Cochrane Library, 4,390 from Google Scholar, 68 from MEDLINE/PubMed, and 34 from Scopus), leading to the even-

**Table 1 - Study features.**

	Plaisance (2000)	Wolke (2003)	Plaisance (2004)	Aufderheide (2005)	Pirrallo (2005)	ResQ (2011)	ROC PRIMED (2011)
Patients	21	210	400	230	22	2470	8718
Comparisons	ITD + ACD-CPR vs sham ITD + ACD-CPR	ITD + ACD-CPR vs standard CPR	ITD + ACD-CPR vs sham ITD + ACD-CPR	ITD + standard CPR vs sham ITD + standard CPR	ITD + standard CPR vs sham ITD + standard CPR	ITD + ACD-CPR vs standard CPR	ITD + ACD-CPR vs sham ITD + ACD-CPR
Maximum follow-up	1 month	In-hospital	In-hospital	1 year	In-hospital	1 year	In-hospital
Multicenter setting	Yes	No	Yes	Yes	Yes	Yes	Yes
Allocation concealment	Sham	Randomized code broken after initial resuscitation	Sham	Sham	Sham	Randomized code broken after initial resuscitation	Sham
Randomization list generation	Computer	Computer	Unclear	Computer	Computer	Computer	Unclear
Selection bias	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
Performance bias	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
Attrition bias	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Detection bias	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
Potential conflicts of interest	Yes	Yes	Yes	Yes	Yes	No	Yes

*ACD = active compression-decompression; CPR = cardiopulmonary resuscitation; ITD = impedance threshold device.*

tual inclusion of 7 trials (11,254 patients). Included studies were published between 2000 and 2011 (11-12, 22-26), varying in size between 21 and 8,718 subjects (*Table 1*) (12, 22), with follow-up limited to the emergency or hospital setting in all but three reports (11, 22, 25). Study quality was in general high. Notably, all but one trial report was coauthored by one of the co-inventors of ITD (12). Patient and procedural features were largely similar (*Table 2*), with average age ranging between 58 and 67 years, CPR duration between 28 and 45 minutes, and ventricular fibrillation or ventricular tachycardia as initial rhythm spanning from 0 % to 40 %.

Meta-analysis for ROSC suggested an overall neural effect of ITD (OR = 1.02 [0.94-1.11], p for effect = 0.598; OR = 1.17 [0.96-1.43], p for effect = 0.114; p for heterogeneity = 0.055, I-squared = 51 %, using fixed- and random-effects models respectively), with evidence of small study effects (p = 0.071) (*Figures 1 and 2*). Accordingly, ITD did not impact significantly on the li-

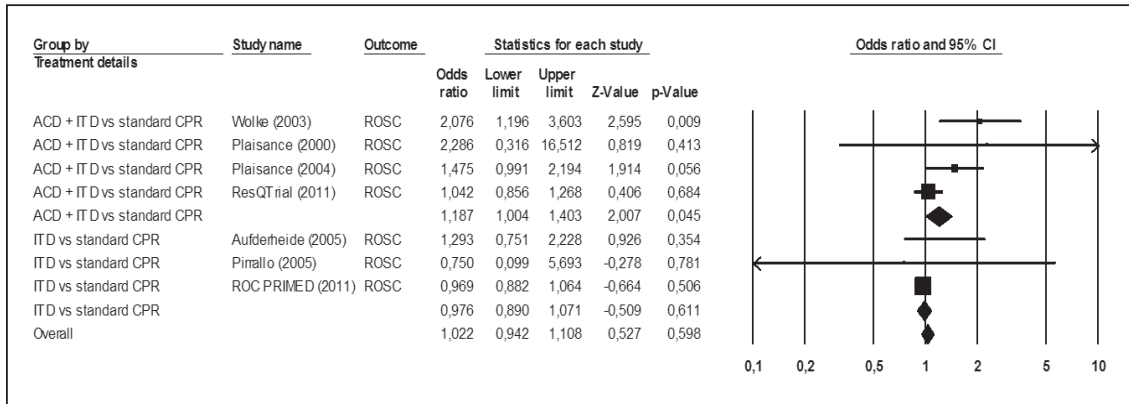
kelihood of favorable neurologic outcome (OR = 1.12 [0.95-1.30], p for effect = 0.172; OR = 1.56 [0.97-2.50], p for effect = 0.065; p for heterogeneity = 0.011, I-squared = 67 %, using fixed- and random-effects models respectively), or survival at the longest available follow-up (OR = 1.09 [0.95-1.25], p for effect = 0.236; OR = 1.22 [0.94-1.58], p for effect = 0.127; p for heterogeneity = 0.236, I-squared = 27 %, using fixed- and random-effects models respectively), with some evidence for small study effects for both outcomes (respectively p = 0.107 and p = 0.058) (*Figures 3, 4, 5 and 6*).

As some studies had combined ITD with ACD-CPR while others had not, and this association has been considered very important to maximize ITD efficacy, we then performed an exploratory analysis stratifying trials according to the concomitant use of ITD and ACD-CPR. This subgroup analysis showed that use of both ITD and ACD-CPR was associated with a significant increase in the rate of ROSC (OR = 1.19 [1.00-1.40], p for effect = 0.045, using the fixed-effects

**Table 2** - Patient and procedural features.

	Plaisance (2000)	Wolke (2003)	Plaisance (2004)	Aufderheide (2005)	Pirrallo (2005)	ResQ (2011)	ROC PRIMED (2011)
Age (years)	58	67	59	66	61	60	67
Men	71 %	62 %	67 %	61 %	59 %	66 %	64 %
Witnessed arrest	66 %	75 %	75 %	55 %	48 %	56 %	48 %
Bystander CPR	20 %	28 %	10 %	27 %	27 %	43 %	38 %
CPR duration (minutes)	28	35	28	31	45	28	NA
Call to BLS arrival time (minutes)	7	6	9	5	NA	7	6
Call to ALS arrival time (minutes)	20	NA	18	7	9	NA	9
Call to device arrival time (minutes)	NA	10	NA	12	19	7	NA
Initial rhythm							
VF	0 %	40 %	25 %	26 %	18 %	33 %	24 %
Asystole	100 %	30 %	71 %	51 %	45 %	46 %	44 %
PEA	0 %	30 %	4 %	23 %	32 %	21 %	24 %

ALS = advanced life support; BLS = basic life support; CPR = cardiopulmonary resuscitation; NA = not available; PEA = pulseless electrical activity; VF = ventricular fibrillation.



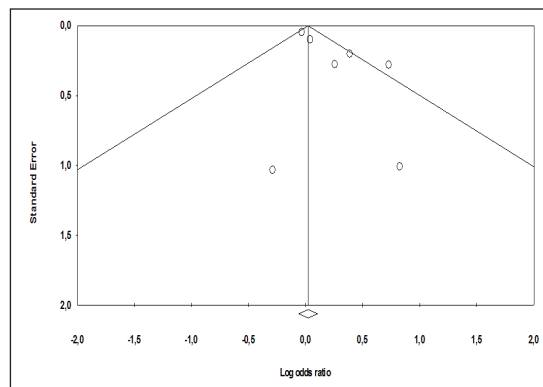
**Figure 1** - Forest plot for return of spontaneous circulation (ROSC), reporting individual and summary effect estimates based on fixed effects. ACD = active compression-decompression; CI = confidence interval; CPR = cardiopulmonary resuscitation; ITD = impedance threshold device.

model), favorable neurologic outcome (OR = 1.60 [1.14-2.25], p for effect = 0.006, using the fixed-effects model), or overall survival (OR = 1.52 [1.11-2.08], p for effect = 0.009, using the fixed-effects model). Conversely, ITD alone was not beneficial for ROSC, favorable neurologic outlook, or survival (respectively OR = 0.98 [0.89-1.07], p for effect = 0.611, 1.01 [0.85-1.21], p for effect = 0.903, and 1.01 [0.86-1.17], p for effect = 0.950, using the fixed-effects model). This interaction between treatment effect (expressed as the logarithm of the OR) and use of ACD-CPR together with ITD was confirmed at meta-regression analysis (b = 0.195, p = 0.045 in favor of ITD + ACD-CPR vs ITD alone for ROSC; b = 0.500, p = 0.018 for favorable neurologic outcome; and b = 0.413, p = 0.021 for overall survival).

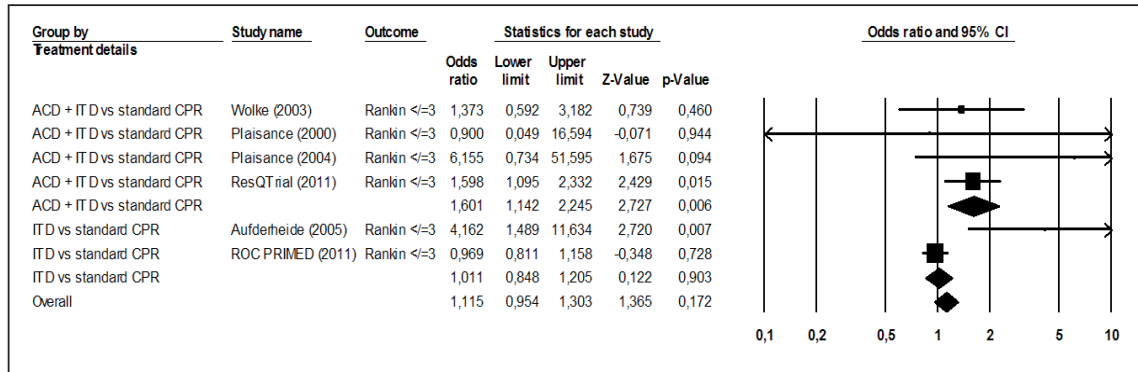
**DISCUSSION**

This systematic review and meta-analysis, providing a comprehensive and updated appraisal of the current evidence base on the role of ITD in patients with OOHCA undergoing CPR, has the following implications:

- a) the totality of the evidence, including a mix of trials exploiting ITD alone with studies in which ITD was used together with ACD-CPR, shows no meaningful impact of ITD use on the likelihood of ROSC, favorable neurologic outcome, or long-term mortality;
- b) the available data are highly skewed, with the largest and most recent trial greater than the sum of all the other trials, together with evidence of significant statistical heterogeneity and small study effects;
- c) exploratory analysis based on the combination of ITD plus ACD-CPR suggests



**Figure 2** - Funnel plot for return of spontaneous circulation (ROSC), p = 0.071.



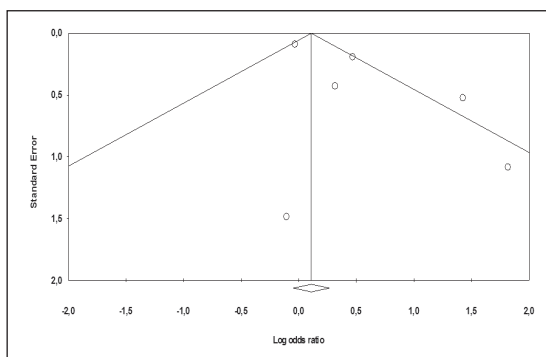
**Figure 3** - Forest plot for favorable neurologic outcome, reporting individual and summary effect estimates based on fixed effects. ACD = active compression-decompression; CI = confidence interval; CPR = cardiopulmonary resuscitation; ITD = impedance threshold device.

that this combo strategy is associated with favorable clinical results in comparison to a strategy based on ACD-CPR alone or standard CPR;

d) conversely, exploratory subgroup analysis focusing on the use of ITD only confirms overall results against a clinically beneficial effect of ITD when used without ACD-CPR.

Despite remarkable improvements in the primary prevention of the most common causes of OOHCA, this condition remains common and ominous (27).

Both in witnessed and unwitnessed OOHCA several precious minutes are often wasted before effective BLS is started,

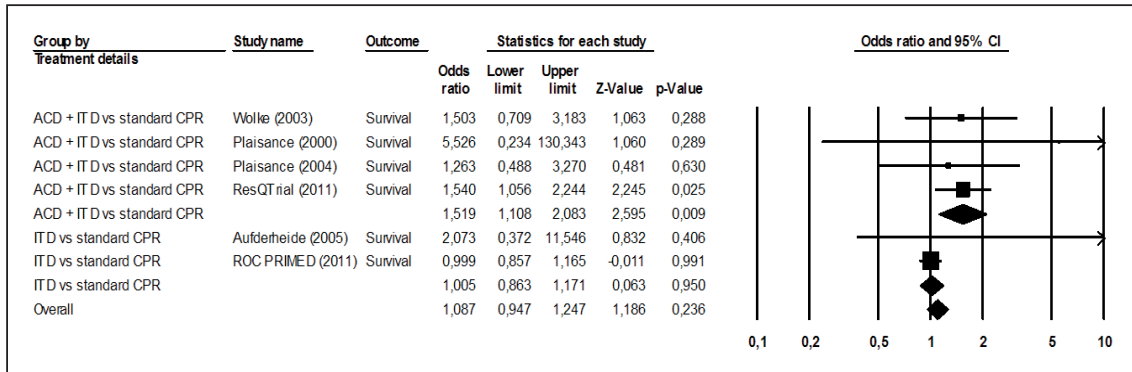


**Figure 4** - Funnel plot for favorable neurologic outcome ( $p = 0.107$ ).

translating into unsatisfactory clinical results.

Several strategies have been proposed, tested in animal studies, and then trialed formally in humans, with the ultimate goal of saving lives and improving neurologic prognosis. These include mechanical chest compression devices, ITD, ACD-CPR, hypothermia, emergency extra-corporeal membrane oxygenation, vasopressor, inotropic and antiarrhythmic drugs, and emergency coronary angiography (28). The evidence base for these approaches is heterogeneous, with some procedures supported by a large and homogenous evidence base (e.g. hypothermia) and others still relying on observational evidence at best (e.g. emergency coronary angiography).

Accordingly, decision-makers envisioning the adoption of any one of the above approaches face a difficult challenge, as they wish to maximize their chances to improve what is often a very dismal prognosis, and the ethical and clinical imperative to avoid useless or potentially harmful interventions. This may hold even truer for the decision of whether to use or not the ITD. The ITD is a rather simple and relatively inexpensive device consisting of a valve interconnected between the patient airways and



**Figure 5** - Forest plot for survival at longest available follow-up, reporting individual and summary effect estimates based on fixed effects. ACD = active compression-decompression; CI = confidence interval; CPR = cardiopulmonary resuscitation; ITD = impedance threshold device.

the ventilation means used during CPR. Beside potentially decreasing intrathoracic pressure during the release phase of a chest compression cycle, while improving venous return to the heart and thus cardiac output, it guides CPR by providing visual guidance on optimal ventilation timing to BLS and ALS providers (5).

The concept behind ITD is intriguing and the experimental evidence base in animals and in pilot human trials rather compelling (4-5, 29).

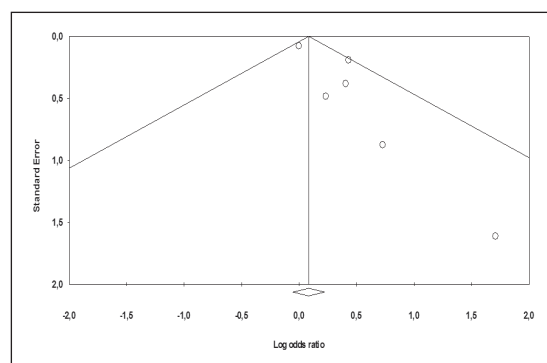
There is a dark side of the moon, though. Despite favorable results from smaller randomized trials (10), the two largest and most recent trials have provided patently conflicting evidence, with the largest trial (ROC PRIMED, 8,717 patients) evidently demonstrating that ITD alone has no meaningful clinical effect in comparison to a sham device in patients with OOHCA undergoing CPR (12).

This is clearly at odds with the favorable results provided by the second largest trial, which combined ITD with ACD-CPR and compared it with standard CPR for OOHCA (ResQ, 2,470 subjects) (11). Notably, a pooled summary effect estimate confirms (and is dominated by) the ROC PRIMED trial results, with ITD appearing associated

with non-significant changes on prognosis. Conversely, pooled analysis of trials using both ITD and ACD-CPR suggest that this combo might be significantly beneficial.

It is difficult to define which is the most appropriate attitude towards such clinical conundrum. One approach would be to disregard altogether ITD as ineffective (at least as long as the overall analysis is concerned).

This decision could be revised in case a (very unlikely) future trial, larger than the ROC PRIMED one, shifts the balance of overall effect estimate in favor of ITD. Another approach would be to trust (possibly too naively) our subgroup analysis, and



**Figure 6** - Funnel plot for survival at longest available follow-up ( $p = 0.058$ ).

recommend routine use of both ICD and ACD-CPR to save lives and improve neurologic prognosis. A middle ground choice would be to envision a more selective and individualized use of ITD and ACD-CPR in specific patients with OOHCA, who are not deemed extremely unlikely to achieve ROSC nor who quickly regain spontaneous circulation.

The latter approach, based on a tailored use of ITD and ACD-CPR, would make sense given the extreme heterogeneity of patients with OOHCA (30).

Probably ACD may allow to perform a more accurate number of chest compressions per minute, while standard rescuers may often perform too many and too shallow compressions per minute, without eliciting adequate thoracic elastic recoil. Indeed, even minor improvements in ROSC, neurologic prognosis and long-term survival in a subset of patients with OOHCA could have dramatic implications at a societal level, in keeping with the ominous impact that this condition still has.

Finally, in favor of the hypothesis that ITD plus ACD-CPR is clinically beneficial are also preliminary data on the role of ITD in conscious but hypotensive patients (8). Conversely, meta-analyses of trials focusing solely on ACD-CPR do support their role during cardiac arrest, thus partially undermining the credibility of the favorable results hereby reported for ITD combined with ACD-CPR (31).

Limitations of this work include those inherent to any systematic review (17), and the risk of type I error and data mining, which is typical of subgroup analysis not based on hypotheses explicitly stated a priori.

In addition, all included trials were performed in settings where operators and services were highly qualified and resourceful, thus results obtained in such scenarios cannot be readily translated into different environments or healthcare contexts.

## CONCLUSION

The evidence base on ITD in patients with OOHCA undergoing CPR is apparently inconclusive, with a neutral impact of clinically relevant outcomes. However, exploratory analysis focusing on the combined use of ITD plus ACD-CPR suggests that this combo may be useful to increase the likelihood of ROSC, favorable neurologic outcome, and long-term survival.

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**Cite this article as:** Biondi-Zoccai G, Abbate A, Landoni G, Zangrillo A, Vincent JL, D'Ascenzo F, Frati G. An updated systematic review and meta-analysis on impedance threshold devices in patients undergoing cardiopulmonary resuscitation. *Heart, Lung and Vessels*. 2014; 6(2): 105-113.

**Source of Support:** Nil. **Disclosures:** None declared.

