International standards for medical devices – can they produced and implemented globally?

A clinical perspective on aspirational care for our global patients with an optimistic look at overcoming potential impediments to these processes

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17 April 2024

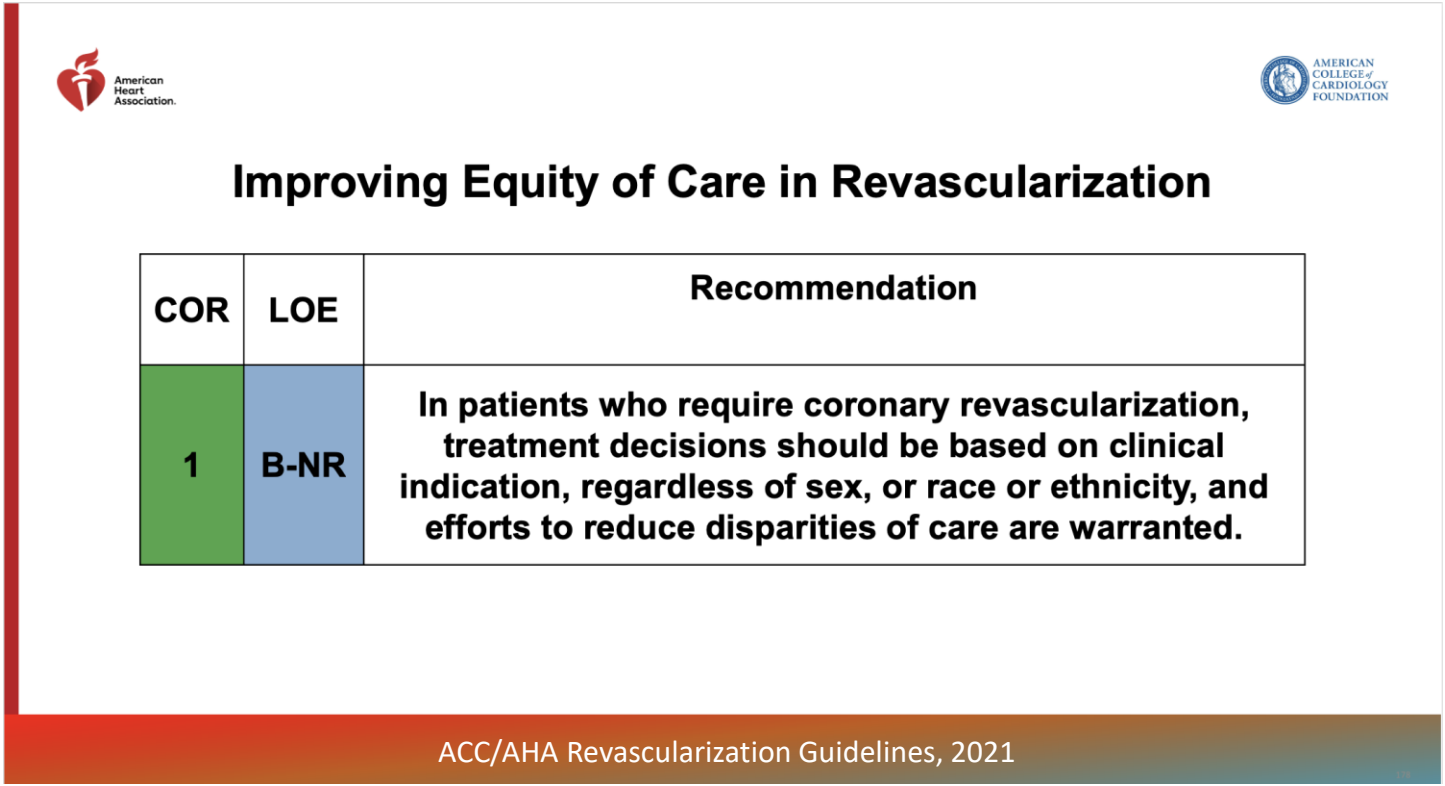
ESC
European Society of Cardiology

An honest confession…

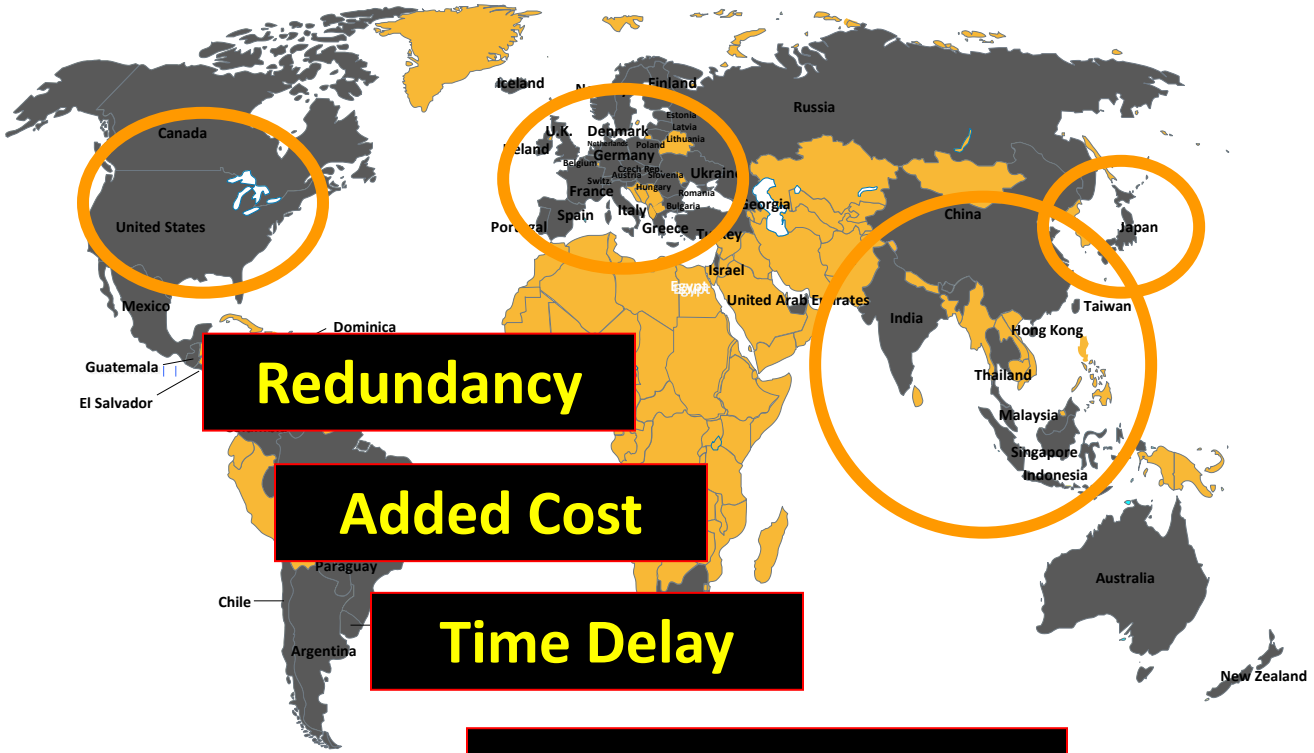
- As a clinician/educator/researcher, I take the concept of “expertise” very seriously…
- And in this specific topic, I have (truthfully) have very little of it!
- So what possibly could I add to this conversation that might be of interest?

The traditional model

International standards make intuitive clinical sense!



Historical Evaluation of New Medical Devices



c/o M. Krucoff

How to overcome this? It starts with collaboration

The US EFS Value Proposition
For Devices Ultimately Intended for the US

- Travel & language factors
- Data quality & monitoring considerations
- Available study subjects
- Patient characteristics relevant to the US population
- CE Mark & MDR challenges

Starting earlier in the US

- Early FDA familiarity with the technology
- Consensus on non-clinical test plan
- US IRB approval & site initiation with accelerated operator learning curves

US EFS and non-US studies can be done in parallel

c/o A. Farb, FDA

Can regulatory efforts be harmonized?

Global Harmonization Task Force (1993 – 2012)

GHTF

- Initial effort intended to promote multilateral medical device regulatory convergence

IMDRF International Medical Device Regulators Forum

(2011 – Present)

- Building on the work of GHTF to further accelerate international medical device regulatory harmonization and convergence
- Regulator-driven activities
  - Non-regulators can participate as observers
  - Proposed IMDRF documents are voluntary and incorporate public comments prior to finalization and adoption

Global Harmonization Working Party

- Formed in 1999 to promote regulatory harmonization throughout Asia, and now includes other regions
  - General guidance and specific technical documents
  - Outreach and education to non-member geographies
- US official member 2021 – 2023
- Alignment of harmonization approaches will be important

AHWP
ASIAN HARMONIZATION WORKING PARTY

→

GHWP
Global Harmonization Working Party
Towards Medical Device Harmonization

Harmonization by Doing (HBD)

- Effort started in 2003 by US and Japanese regulators, industry members, and physicians to identify and address challenges associated with the evaluation and availability of cardiovascular devices in both countries
- "Proof of concept" projects involving specific devices or larger clinical/regulatory areas


REVIEW

Rapid Globalization of Medical Device Clinical Development Programs in Japan
— The Case of Drug-Eluting Stents —


REVIEW

Design Strategies for Global Clinical Trials of Endovascular Devices for Critical Limb Ischemia (CLI)
— A Joint USA-Japanese Perspective —

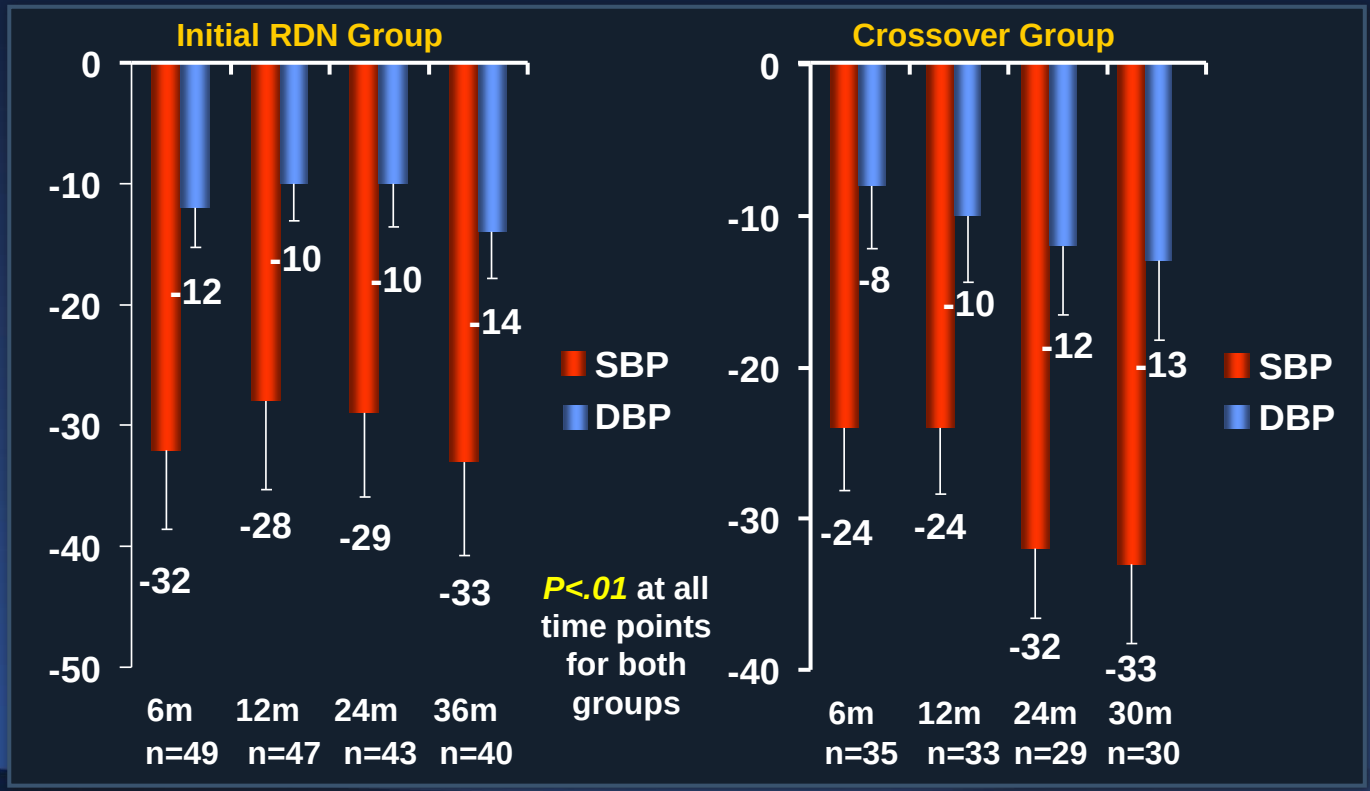
c/o K. Cavanaugh, Jr (FDA)

How can clinicians/researchers make a difference?

- Collaborative working groups/thinktanks, Multinational societies, and Academic research organizations are the NATURAL torchbearers to advocate for our (global) patients

- But do we have a voice that can truly catalyze action (and regulatory action)?

SYMPLICITY HTN-2: Change in Office Blood Pressure through 36-Months Post-Randomization*



* Crossover patients only had 30 months post procedure data

R. Whitbourn, TCT 2013

Cardiovascular Research Foundation

Columbia University Medical Center

NewYork-Presbyterian

Renal Denervation at TCT 2013

Signs of a field poised to explode…

- At TCT this year, we had:
  - Full-day Sunday symposium on RDN
  - Innovation sessions including RDN
  - How-to Session on RDN
  - FDA Town Hall Session on RDN
  - Abstract Subsession on RDN
  - 3 Breakfast Symposia on RDN
  - 1 Dedicated Evening Symposium on RDN, 1-2 others touched on RDN

SYMPLICITY HTN-3 Announcement

MEDTRONIC ANNOUNCES U.S. RENAL DENERVATION PIVOTAL TRIAL FAILS TO MEET PRIMARY EFFICACY ENDPOINT WHILE MEETING PRIMARY SAFETY ENDPOINT

MINNEAPOLIS – January 9, 2014 – Medtronic, Inc. (NYSE: MDT) today announced that its U.S. pivotal trial in renal denervation for treatment-resistant hypertension, SYMPLICITY HTN-3, failed to meet its primary efficacy endpoint. The trial met its primary safety endpoint, and the trial's Data Safety Monitoring Board (DSMB) concluded that there were no safety concerns in the study.

Overnight, the future of RDN became uncertain

Consensus Documents, FDA Advisory Panel

ESC European Society of Cardiology
European Heart Journal (2020) **41**, 1588–1599
doi:10.1093/eurheartj/ehaa121

CURRENT OPINION
Hypertension

Proceedings from the 3rd European Clinical Consensus Conference for clinical trials in device-based hypertension therapies

Felix Mahfoud [1,2]*, Michel Azizi[3,4,5], Sebastian Ewen[1], Atul Pathak [5,6], Christian Ukena[1], Peter J. Blankestijn[7], Michael Böhm[1], Michel Burnier [8], Gilles Chatellier[3,9], Isabelle Durand Zaleski [10], Guido Grassi [11], Michael Joner [12,13], David E. Kandzari[14], Ajay Kirtane [15], Sverre E. Kjeldsen [16], Melvin D. Lobo[17], Thomas F. Lüscher[18,19], John William McEvoy [20], Gianfranco Parati [21], Patrick Rossignol[5,22,23], Luis Ruilope [24], Markus P. Schlaich [25,26], Atif Shahzad [20,27], Faisal Sharif[20,27], Andrew S.P. Sharp[28,29], Horst Sievert[30,31,32,33], Massimo Volpe[34], Michael A. Weber [35], Roland E. Schmieder [36], Costas Tsioufis[37], and William Wijns[38]

ADVISORY COMMITTEE MEETING | IN PERSON

December 4-5, 2018: Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting Announcement

DECEMBER 4 - 5, 2018

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Date: December 4 - 5, 2018

What is an advisory committee?

Advisory committees provide independent expert advice to the FDA on broad scientific topics or on certain products to help the agency make sound decisions based on the available science. Advisory committees make non-binding recommendations to the FDA, which generally follows the recommendations but is not legally bound to do so. Please see, "Advisory Committees Give FDA Critical Advice and the Public a Voice," for more

Renal Denervation Trials v2.0

Managing Variability within Clinical Trials

	Variability	Possible Solutions
	OBP Readings	• Stable baseline (drug wash-in phase) • Ambulatory BP (fully automated and documented), Home BP assessment
	Catheter, Technique, Device Effects	• Optimized catheter effects (studied!) • Consistent operator technique
	Drug changes & Adherence	• Phase II: Placebo controlled off-medications RCT (Stage I-II) • Phase III: Placebo controlled with standardized meds RCT (Uncontrolled/Resistant HTN)

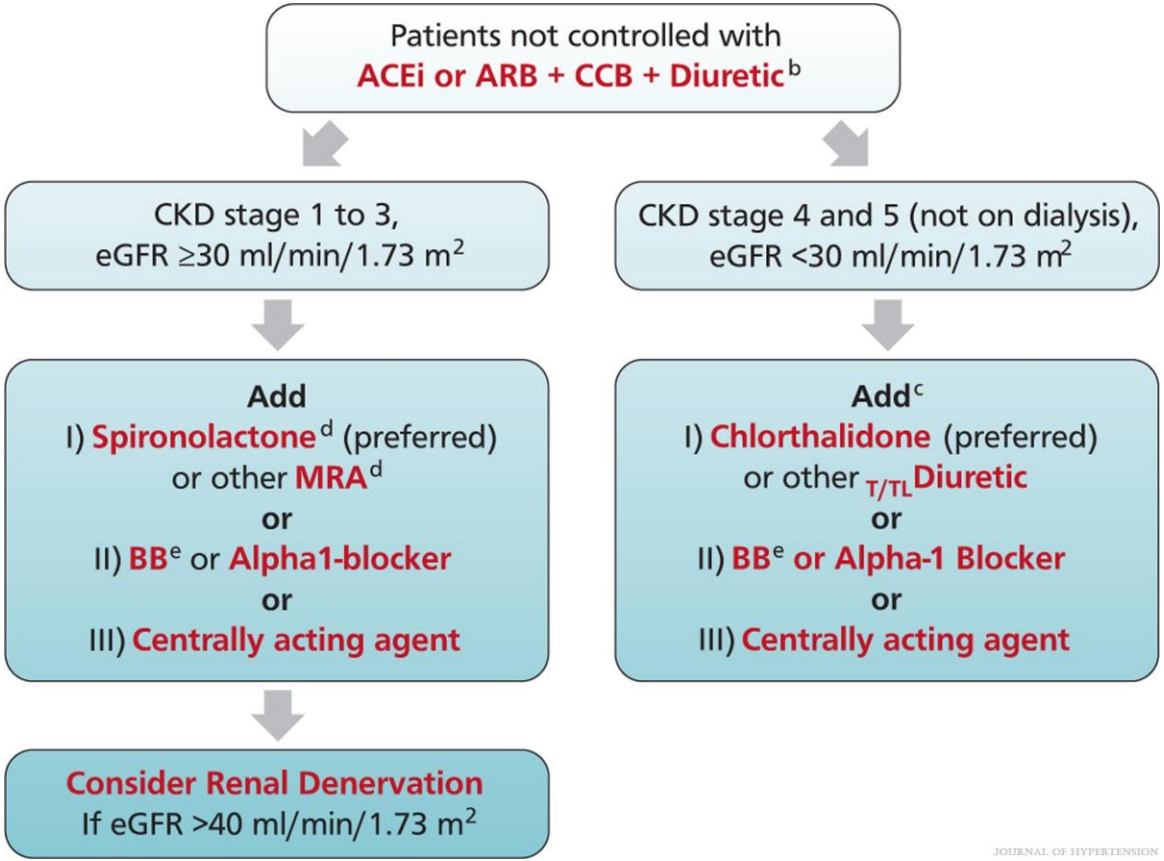
Devices investigated in sham-controlled trials

	Catheter	Design	Access site	Ablation sites	Efficacy confirmed in sham-controlled trial?	
	Radiofrequency					
	Symplicity Spyral (Medtronic)	Multielectrode (4 monopolar gold electrodes), helical design, rapid exchange monorail catheter, 60 seconds per ablation cycle	F (6 Fr)	Main and accessory arteries, including branches (diameter 3-8 mm)	Yes, multiple trials	FDA
	Netrod (Shanghai Golden Leaf Medtec)	Multielectrode (6 electrodes), basket-shaped tip, 120 seconds per ablation cycle	F (8 Fr)	Main and accessory arteries, including branches (diameter 3-12 mm)	Yes, single study (EuroPCR 2023, publication pending)	
	Iberis 2nd-generation (AngioCare and Terumo)	Multielectrode (4 monopolar electrodes), helical design, over-the-wire catheter, 60 seconds per ablation cycle, 90 cm catheter length for transfemoral and 160 cm for transradial RDN	F/R (6 Fr)	Main and accessory arteries, including branches (diameter 3-8 mm)	Yes, single study (CIT Congress 2023, publication pending)	
	SyMapCath I	Steerable monoelectrode stimulation and ablation catheter, stimulation time 20-120 seconds, 120 seconds per ablation cycle	F (6-7 Fr)	Main renal arteries	Yes, single study	
	Ultrasound					
	TIVUS (SoniVie)	Unidirectional steerable or multidirectional, over-the-wire, 30 seconds per emission	F (6 Fr)	Main and accessory arteries (diameter ≥4 mm)	No	
	Paradise (ReCor Medical)	Piezoelectric ceramic transducer within a fluid-cooled, low-pressure balloon, over-the-wire, 7 seconds per emission	F (7 Fr)	Main and accessory arteries (different catheter sizes for diameters of 3-8 mm)	Yes, multiple studies	FDA
	Neurolysis					
	Peregrine (Ablative Solutions)	3 extendable microneedles	F (7 Fr)	Main and accessory arteries (4-7 mm)	No, TARGET-BP I ongoing	

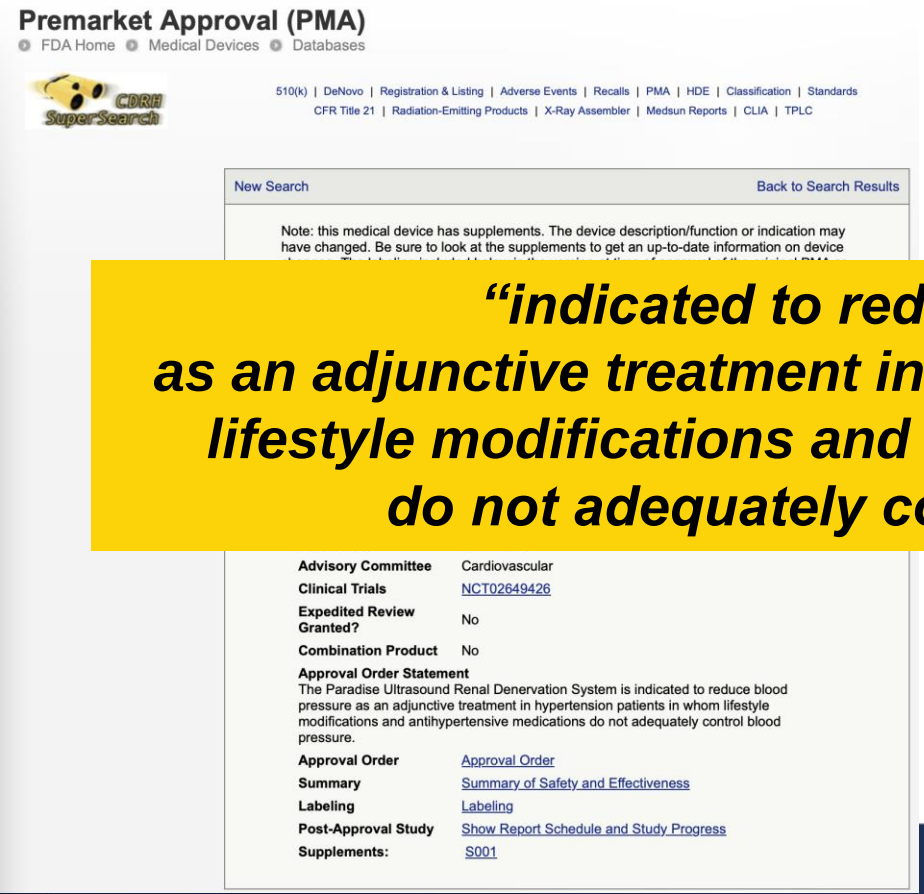
Lauder L *et al. EuroIntervention*. 2024 (accepted).

c/o F. Mahfoud

2023 European Society of Hypertension Guidelines



US FDA Device Approvals for RDN



Premarket Approval (PMA)

FDA Home | Medical Devices | Databases

510(k) | DeNovo | Registration & Listing | Adverse Events | Recalls | PMA | HDE | Classification | Standards
CFR Title 21 | Radiation-Emitting Products | X-Ray Assembler | Medsun Reports | CLIA | TPLC

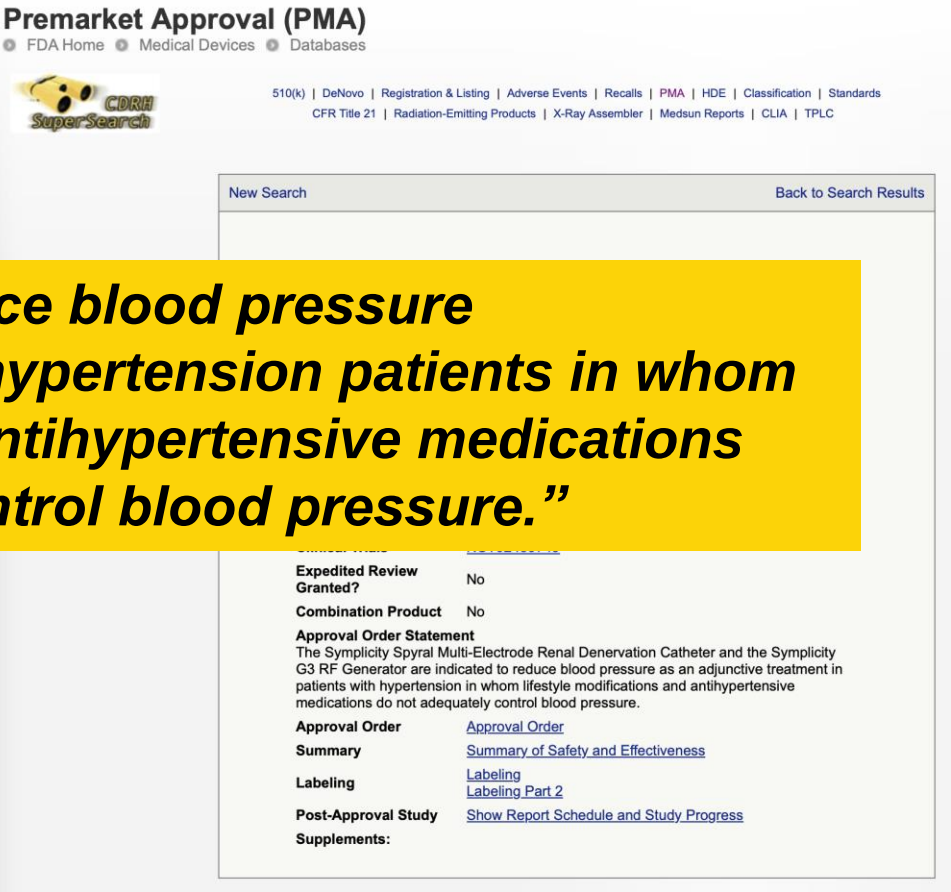
New Search | Back to Search Results

Note: this medical device has supplements. The device description/function or indication may have changed. Be sure to look at the supplements to get an up-to-date information on device

Advisory Committee	Cardiovascular
Clinical Trials	NCT02649426
Expedited Review Granted?	No
Combination Product	No

Approval Order Statement
The Paradise Ultrasound Renal Denervation System is indicated to reduce blood pressure as an adjunctive treatment in hypertension patients in whom lifestyle modifications and antihypertensive medications do not adequately control blood pressure.

Approval Order	Approval Order
Summary	Summary of Safety and Effectiveness
Labeling	Labeling
Post-Approval Study	Show Report Schedule and Study Progress
Supplements:	S001



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New Search | Back to Search Results

Expedited Review Granted?	No
Combination Product	No

Approval Order Statement
The Symplicity Spyral Multi-Electrode Renal Denervation Catheter and the Symplicity G3 RF Generator are indicated to reduce blood pressure as an adjunctive treatment in patients with hypertension in whom lifestyle modifications and antihypertensive medications do not adequately control blood pressure.

Approval Order	Approval Order
Summary	Summary of Safety and Effectiveness
Labeling	Labeling Labeling Part 2
Post-Approval Study	Show Report Schedule and Study Progress
Supplements:	

"indicated to reduce blood pressure as an adjunctive treatment in hypertension patients in whom lifestyle modifications and antihypertensive medications do not adequately control blood pressure."

1st US RDN Patient treated Commercially Post-Approval

Conclusions / Points for discussion

- International standards for medical devices can certainly be produced or already exist (created by respective experts)
  - Manufacturing (already exists)
  - Pre-clinical testing: can we move to “regulatory reliance”?
  - Early Feasibility: why not think globally?
  - Approval studies (balance “least burdensome” with “clinical believability”)
  - Meaningful post-approval studies (think DanGer shock aspirationally)
- Implementation may be the greatest challenge
  - Regulations are typically based upon country-specific laws
  - *Collaborative relationships between regulators / industry / societies*