JACC: CARDIOVASCULAR IMAGING
VOL. 14, NO. 3, 2021

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

Worldwide Diagnostic Reference Levels for Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging

Findings From INCAPS

Cole B. Hirschfeld, MD,[a] Maurizio Dondi, MD,[b] Thomas N.B. Pascual, MD,[b] Mathew Mercuri, PhD,[c,d] Joao Vitola, MD, PhD,[e] Ganesan Karthikeyan, MD,[f] Nathan Better, MD,[g] John J. Mahmarian, MD,[h] Salah E. Bouyoucef, MD,[i] Henry Hee-Seung Bom, MD, PhD,[j] Vikram Lele, MD,[k] Vincent Peter C. Magboo, MD,[l,m] Erick Alexánderson, MD,[n,o] Adel H. Allam, MD,[p] Mouaz H. Al-Mallah, MD, MS,[h] Albert Flotats, MD,[q] Scott Jerome, DO,[r,s] Philipp A. Kaufmann, MD,[t] Osnat Luxenburg, MD, MPH, MBA,[u,v] S. Richard Underwood, DM,[w,x] Madan M. Rehani, PhD,[y] Jenia Vassileva, PhD,[z] Diana Paez, MD,[b] Andrew J. Einstein, MD, PhD,[aa,bb]
for the INCAPS Investigators Group

ABSTRACT

OBJECTIVES This study sought to establish worldwide and regional diagnostic reference levels (DRLs) and achievable administered activities (AAAs) for single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI).

BACKGROUND Reference levels serve as radiation dose benchmarks to compare individual laboratories against aggregated data, helping to identify sites in greatest need of dose reduction interventions. DRLs for SPECT MPI have previously been derived from national or regional registries. To date there have been no multiregional reports of DRLs for SPECT MPI from a single standardized dataset.

METHODS Data were submitted voluntarily to the INCAPS (International Atomic Energy Agency Nuclear Cardiology Protocols Study), a cross-sectional, multinational registry of MPI protocols. A total of 7,103 studies were included. DRLs and AAAs were calculated by protocol for each world region and for aggregated worldwide data.

RESULTS The aggregated worldwide DRLs for rest-stress or stress-rest studies employing technetium Tc 99m-labeled radiopharmaceuticals were 11.2 mCi (first dose) and 32.0 mCi (second dose) for 1-day protocols, and 23.0 mCi (first dose) and 24.0 mCi (second dose) for multiday protocols. Corresponding AAAs were 10.1 mCi (first dose) and 28.0 mCi (second dose) for 1-day protocols, and 17.8 mCi (first dose) and 18.7 mCi (second dose) for multiday protocols. For stress-only technetium Tc 99m studies, the worldwide DRL and AAA were 18.0 mCi and 12.5 mCi, respectively. Stress-first imaging was used in 26% to 92% of regional studies except in North America where it was used in just 7% of cases. Significant differences in DRLs and AAAs were observed between regions.

CONCLUSIONS This study reports reference levels for SPECT MPI for each major world region from one of the largest international registries of clinical MPI studies. Regional DRLs may be useful in establishing or revising guidelines or simply comparing individual laboratory protocols to regional trends. Organizations should continue to focus on establishing standardized reporting methods to improve the validity and comparability of regional DRLs.
(J Am Coll Cardiol Img 2021;14:657-65) © 2021 by the American College of Cardiology Foundation.

ISSN 1936-878X/$36.00
https://doi.org/10.1016/j.jcmg.2020.06.029

ABBREVIATIONS AND ACRONYMS

AAA = achievable administered activity

CT = computed tomography

DRL = diagnostic reference level

IAEA = International Atomic Energy Agency

ICRP = International Commission on Radiological Protection

MPI = myocardial perfusion imaging

PET = positron emission tomography

SPECT = single-photon emission computed tomography

Tc-99m = technetium Tc 99m

Tl-201 = thallium Tl 201

Myocardial perfusion imaging (MPI) is an effective noninvasive method to diagnose and risk-stratify patients with coronary artery disease, but it may also account for one-fifth of the total burden of radiation to the U.S. population from medical imaging (1-3). The rising use of medical imaging in recent decades has ignited concerns over the effects of population exposure to ionizing radiation (3-6). In response, numerous organizations have published guidelines to define best practices and detailed patient selection criteria to optimize dose reduction (7-14). Recent data have shown that the majority of U.S. facilities continue to operate above dose levels that could be attained through compliance with guideline recommendations, which suggests that adherence to best practices may be suboptimal (15,16).

Another method of reducing radiation exposure is to identify facilities where patient doses are unusually high, such that implementing targeted dose reduction strategies would have the greatest impact. This idea was first suggested in 1991 by the International Commission on Radiological Protection (ICRP) in its publication 60 (17), which introduced the concept of "investigational levels" to be set for common diagnostic procedures. In 1996, this term became known as the diagnostic reference level (DRL) in ICRP publication 73 (18). In both diagnostic radiology and nuclear medicine, DRLs represent a benchmark, above which outliers may be identified for closer examination of practices and protocols (18-22). DRLs can be established at local or national levels and should ideally be derived from distributions of actual patient examinations (20). The implementation of DRLs as a dose reduction strategy is widely endorsed by professional societies and national agencies for radiological protection (7-9,11,14,22-25) and is required by the International Safety Standards (26,27). Interventions to improve optimization in facilities that fall above the DRL are addressed in publications and guidelines from numerous organizations (7-11,13,14,19,22). More recently, the concept of achievable administered activity (AAA), which corresponds to the median (50th percentile) of a distribution of doses, has emerged as a target for further dose optimization in facilities that fall below the DRL (7,19).

As one of the largest contributors to medical radiation exposure, it is vital to establish DRLs for single-photon emission computed tomography (SPECT) MPI dose optimization in every world region. Unfortunately, efforts to derive and use DRLs in cardiology and nuclear medicine lag behind other fields, with a

From the [a]Department of Medicine, Columbia University Irving Medical Center and NewYork-Presbyterian Hospital, New York, New York, USA; [b]Section of Nuclear Medicine and Diagnostic Imaging, Division of Human Health, International Atomic Energy Agency, Vienna, Austria; [c]Division of Emergency Medicine, McMaster University, Hamilton, Ontario, Canada; [d]Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada; [e]Quanta Diagnóstico e Terapia, Curitiba, Brazil; [f]Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India; [g]Department of Nuclear Medicine, Royal Melbourne Hospital and University of Melbourne, Melbourne, Victoria, Australia; [h]Department of Cardiology, Houston Methodist DeBakey Heart and Vascular Center, Houston, Texas, USA; [i]Department of Nuclear Medicine, Centre Hospitalo-Universitaire de Bab El Oued, Alger, Algeria; [j]Department of Nuclear Medicine, Chonnam National University Medical School, Gwangju, Republic of Korea; [k]Department of Nuclear Medicine and PET-CT, Jaslok Hospital and Research Centre, Mumbai, India; [l]Department of Physical Sciences and Mathematics, University of the Philippines, Quezon City, Philippines; [m]Department of Nuclear Medicine, University of Santo Tomas Hospital, Manila, Philippines; [n]Departamento de Cardiología Nuclear, Instituto Nacional de Cardiología "Ignacio Chávez", Mexico City, Mexico; [o]Department of Physiology, School of Medicine, Universidad Nacional Autónoma de México, Mexico City, Mexico; [p]Cardiology Department, Al Azhar University, Cairo, Egypt; [q]Nuclear Medicine Department, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; [r]Intersocietal Accreditation Commission, Ellicott City, Maryland, USA; [s]Division of Cardiovascular Medicine, Department of Medicine, University of Maryland, Baltimore, Maryland, USA; [t]Department of Nuclear Medicine and Cardiac Imaging, University Hospital Zurich, Zurich, Switzerland; [u]Medical Technology, Health Information and Research Directorate, Ministry of Health, Jerusalem, Israel; [v]Israeli Center for Technology Assessment in Health Care, Gertner Institute for Epidemiology and Health Policy Research, Tel Hashomer, Israel; [w]National Heart and Lung Institute, Imperial College London, London, United Kingdom; [x]Department of Nuclear Medicine, Royal Brompton and Harefield Hospitals, London, United Kingdom; [y]Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts, USA; [z]Radiation Protection of Patients Unit, International Atomic Energy Agency, Vienna, Austria; [aa]Seymour, Paul, and Gloria Division of Cardiology, Department of Medicine, Columbia University Irving Medical Center and NewYork-Presbyterian Hospital, New York, New York, USA; and the [bb]Department of Radiology, Columbia University Irving Medical Center and NewYork-Presbyterian Hospital, New York, New York, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received March 12, 2020; revised manuscript received June 3, 2020, accepted June 4, 2020.

TABLE 1 Regional Demographic Data for SPECT MPI Studies

	Africa	Asia	Europe	Latin America	North America	Oceania	Worldwide
Studies*	330 (5)	1,345 (19)	2,187 (31)	1,055 (15)	1,754 (25)	432 (6)	7,103
Male, %	60	61	61	58	57	55	59
Countries	6	18	27	10	2	2	65
Labs	12	69	101	36	54	34	306
Facility type†							
Hospital inpt	–	71 (5)	66 (3)	57 (5)	32 (2)	29 (7)	255 (4)
Hospital opt	25 (8)	–	45 (2)	–	187 (11)	–	257 (4)
Hospital mixed inpt/opt	163 (49)	1,259 (94)	1,659 (76)	522 (49)	778 (44)	269 (62)	4,650 (65)
Opt with physician practices	70 (21)	15 (1)	31 (1)	181 (17)	529 (30)	83 (19)	909 (13)
Opt imaging-only	72 (22)	–	386 (18)	295 (28)	228 (13)	51 (12)	1,032 (15)
Protocol†							
Stress-rest (1 day)	48 (15)	391 (29)	797 (36)	212 (20)	22 (1)	56 (13)	1,526 (21)
Stress-rest (multiday)	145 (44)	238 (18)	599 (27)	166 (16)	57 (3)	2 (0)	1,207 (17)
Rest-stress (1 day)	8 (2)	397 (30)	62 (3)	307 (29)	1,571 (90)	284 (66)	2,629 (37)
Rest-stress (multiday)	20 (6)	47 (3)	271 (12)	316 (30)	52 (3)	35 (8)	741 (10)
Stress-only	109 (33)	272 (20)	458 (21)	54 (5)	52 (3)	55 (13)	1,000 (14)
Radioisotope†							
Tc-99m	330 (100)	1,071 (80)	2,123 (97)	1,030 (98)	1,730 (99)	404 (94)	6,688 (94)
Tl-201	–	169 (13)	58 (3)	14 (1)	–	20 (5)	261 (4)
Dual isotope	–	105 (8)	6 (0)	11 (1)	24 (1)	8 (2)	154 (2)

Values are n (%) or n, unless otherwise indicated. *Percentage of row total. †Percentage of column total.
inpt = inpatient; opt = outpatient; Tc-99m = technetium Tc 99m; Tl = thallium Tl 201.

limited availability of quality data 7,22). Furthermore, there is no standard methodology for reporting DRLs for SPECT MPI between regions, or within a region, making efforts to compare DRLs challenging and imprecise. The European Commission observed that the comparison of DRLs for myocardial perfusion studies was especially difficult due to differences in the reporting of protocols between European countries (8). ICRP publication 135 states that "it is difficult to compare administered activities without knowing the precise protocol used" (19). Alkhybari et al. (28) published a systematic review of DRL methods for positron emission tomography (PET)/CT and SPECT/CT in which they identified major regional and national discrepancies in the methods used to calculate and report DRLs and recommended more robust standards to improve the comparability of international reference levels.

In this analysis, we calculate and compare regional reference levels (DRLs and AAAs) for SPECT MPI using a single international registry of MPI studies. The International Atomic Energy Agency (IAEA) coordinated a cross-sectional study to collect data on MPI from facilities around the globe called the INCAPS (IAEA Nuclear Cardiology Protocols Study). Drawn from worldwide INCAPS data, this report constitutes the first multiregional report of reference levels for SPECT MPI.

METHODS

Methods of the INCAPS study have been described in detail previously (15). A cross-sectional study was conducted in which facilities performing nuclear MPI were asked to report details of every patient scan performed during a single week from March 18 to April 22, 2013. Facilities were identified through registration with the IAEA as well as other local and international professional organizations. Participation in the registry was on a voluntary basis. Studies utilizing PET, studies that performed rest-only imaging, and studies performed on patients <18 years of age were excluded from this analysis.

Regions were defined as Africa, Asia, Europe, Latin America, North America, and Oceania. Registry data in this analysis included information about patient demographics, facility practice setting, study protocol, radiopharmaceuticals, and administered activity. Study protocols were differentiated by sequence and timing. Protocol sequences were defined as stress-rest (stress imaging followed by rest imaging), rest-stress (rest imaging followed by stress imaging), and stress-only. Studies were further distinguished by study timing (1 day vs. multiple days), and dose (first dose vs. second dose). Radioisotopes used in MPI studies were technetium Tc 99m (Tc-99m), thallium Tl 201 (Tl-201), or dual isotope studies (Tl-201 in the first dose

TABLE 2 Number of SPECT MPI Protocols Submitted by Each Region

	Africa	Asia	Europe	Latin America	North America	Oceania	Worldwide
Tc-99m rest-stress or stress-rest, 1 day	56	664	832	495	1,569	327	3,943
Tc-99m rest-stress or stress-rest, 2 days	165	285	870	482	109	37	1,948
Tc-99m stress-only	109	122	421	53	52	40	797
Tl-201, 1 injection	–	150	37	1	–	15	203
Tl-201, 2 injections	–	19	21	13	–	5	58
Dual isotope	–	105	6	11	24	8	154
Totals	330	1,345	2,187	1,055	1,754	432	7,103

Values are n.
MPI = myocardial perfusion imaging; SPECT = single-photon emission computed tomography; other abbreviations as in Table 1.

and Tc-99m in the second dose). Tc-99m rest-stress and stress-rest studies were grouped together and we did not distinguish between Tc-99m radiotracers (tetrofosmin vs. sestamibi) in this analysis.

The DRL was calculated as the 75th percentile of the distribution of administered activities in each individual category, whereas the AAA was calculated as the median of the distribution. Values at the tail ends of each distribution were included in the analysis. All statistical analyses and calculations were performed using Stata version 15.1 (Stata Corp., College Station, Texas) and Excel (2013; Microsoft, Redmond, Washington). The study was approved by the Columbia University Institutional Review Board, which declared it exempt from the requirements of U.S. federal regulations for the protection of human subjects (45 CFR 46) because the study collected no individually identifiable health information.

RESULTS

A total of 7,911 MPI studies were submitted to the INCAPS database of which 474 PET studies, 299 rest-only studies, 2 pediatric studies, and 33 SPECT cases with incomplete data were excluded, leaving 7,103 SPECT MPI studies for this analysis.

DEMOGRAPHICS. Demographic data are summarized in Table 1. Studies were submitted from 306 individual facilities in 65 countries. Europe contributed the greatest number of total studies (31%) followed by North America (25%), Asia (19%), Latin America (15%), Oceania (6%), and Africa (5%). North America had the greatest ratio of studies per laboratory (33:1), whereas Oceania had the lowest ratio (13:1). More studies were performed on men in all regions (range 55% to 61%). The most common facility type was mixed inpatient-outpatient hospital (65%). The remainder of studies were performed in outpatient imaging-only facilities (15%), outpatient facilities with physician practices (13%), or either a hospital inpatient (4%) or hospital outpatient (4%) setting.

PROTOCOLS AND RADIOISOTOPES. Table 1 also summarizes the breakdown of specific protocols and radioisotopes for each region, whereas Table 2 shows the number of studies for each calculated AAA and DRL category. Rest-stress protocols were used in 90% of North American cases, whereas each of the remaining protocols were used in ≤3% of cases. Stress-first imaging (e.g., stress-rest or stress-only) was used in more than one-quarter of studies in every region (range 26% to 92%) except North America where it was used in only 7% of cases. Stress-only studies accounted for one-third of all studies from Africa and one-fifth from Europe and Asia. Tc-99m-labeled tracers were used in more than 94% of studies in all regions except for Asia where 20% of studies were performed using either Tl-201 or dual isotope protocols.

DRLs AND AAAs. DRLs (Table 3) and AAAs (Table 4, Supplemental Table 1) are summarized for each protocol by world region. The aggregated worldwide DRLs for studies employing Tc-99m-labeled radiopharmaceuticals were 42.7 mCi (regional range 30.0 to 46.0 mCi) for 1-day rest-stress or stress-rest, 46.0 mCi (regional range 37.8 to 64.3 mCi) for multiday rest-stress or stress-rest, and 18.0 mCi (regional range 9.7 to 24.0 mCi) for stress-only studies. The aggregated worldwide AAAs for studies employing Tc-99m-labeled radiopharmaceuticals were 39.1 mCi (regional range 23.0 to 42.2 mCi) for 1-day rest-stress or stress-rest, 36.0 mCi (regional range 32.7 to 61.6 mCi) for multiday rest-stress or stress-rest, and 12.5 mCi (regional range 7.2 to 20.0 mCi) for stress-only studies.

Wide ranges for DRLs and AAAs were observed between regions for every protocol (Central Illustration). The ratio of highest to lowest regional DRL ranged from a factor of 1.5 for 1-day Tc-99m rest-stress or stress-rest protocols to 2.5 for Tc-99m stress-only protocols. The lowest DRLs for Tc-99m studies were observed in stress-only protocols, whereas Oceania had the lowest DRL of just 9.7 mCi and Africa

TABLE 3 Worldwide and Regional DRLs for SPECT MPI From the INCAPS Registry

		Administered Activity, mCi (MBq)						
Protocol	**Dose**	**Africa**	**Asia**	**Europe**	**Latin America**	**North America**	**Oceania**	**Worldwide**
Tc-99m rest-stress or stress-rest, 1 day	1st	11.0 (407)	10.9 (403)	13.3 (492)	15.0 (555)	11.0 (407)	10.1 (374)	11.2 (414)
	2nd	20.0 (740)	30.0 (1,110)	22.0 (814)	32.0 (1,184)	33.9 (1,254)	29.7 (1,099)	32.0 (1,184)
Tc-99m rest-stress or stress-rest, 2 days	1st	27.0 (999)	24.5 (905)	19.0 (703)	25.0 (925)	32.4 (1,199)	22.6 (836)	23.0 (851)
	2nd	27.0 (999)	25.0 (925)	19.1 (706)	25.0 (925)	32.4 (1,199)	24.8 (918)	24.0 (888)
Tc-99m stress-only	1st	24.0 (888)	12.6 (466)	18.0 (666)	24.0 (888)	18.8 (696)	9.7 (359)	18.0 (666)
Tl-201, 1 injection	1st	–	3.2 (118)	3.0 (110)	4.0 (148)	–	2.0 (75)	3.2 (117)
Tl-201, 2 injections	1st	–	3.0 (111)	2.2 (83)	3.0 (111)	–	1.5 (57)	3.0 (111)
	2nd	–	1.2 (44)	1.1 (41)	1.0 (37)	–	0.5 (19)	1.1 (41)
Dual isotope	1st	–	3.0 (111)	3.8 (140)	3.0 (111)	3.0 (112)	2.2 (80)	3.0 (111)
	2nd	–	22.5 (833)	21.6 (800)	20.0 (740)	34.0 (1,258)	13.8 (511)	25.0 (925)

DRL = diagnostic reference level; INCAPS = IAEA Nuclear Cardiology Protocols Study; other abbreviations as in Tables 1 and 2.

and Latin America were the highest at 24.0 mCi. The DRLs and AAAs for 1-day Tc-99m stress-rest or rest-stress protocols were less than the DRLs and AAAs for multiday protocols in every region. However, the aggregated worldwide AAA for 1-day Tc-99m studies was greater than for the AAA for multiday studies because of differences in the proportion of studies contributed by each region for each protocol. For example, North America, which had the highest AAAs, comprised 40% of all 1-day rest-stress or stress-rest studies versus only 6% of all multiday studies, whereas Europe, which had the lowest AAAs, comprised 21% of 1-day studies and 45% of the multiday studies. The mean total administered activities were greater than the regional DRLs in more than 30% of all Tc-99m protocols from North American facilities and in fewer than 30% of all Tc-99m protocols from European facilities (Supplemental Table 2).

DISCUSSION

This report establishes worldwide and regional DRLs and AAAs for SPECT MPI from the INCAPS data. We observed wide ranges for DRLs and AAAs for nearly every protocol, because of significant variations in regional practices. Comparing reference levels from our study to previously published reports was challenging due to limited available data and major differences in methods of data collection, analysis, and reporting between regions. This heterogeneity highlights the need for greater international standardization of methods for establishing and reporting reference levels for SPECT MPI. Regional reference levels may serve an important role in both the evaluation of international practice trends and the optimization of future clinical guidelines.

Recent DRLs for SPECT MPI for U.S. laboratories were published by Becker et al. (29) and in report 172 from the National Council on Radiation Protection and Measurements (7). DRLs for Europe are published in report 180 by the European Commission (8) and for Oceania by the Australian Radiation Protection and Nuclear Safety Agency (30). At present, no regional DRLs for SPECT MPI have been established for Africa, Asia, or South America.

We found that DRLs published previously were generally in accordance with the values published here (7,8,29,30). However, direct comparisons were not always possible given significant differences in the methods of reporting DRLs between regions, owing in part to regional variations of practices, protocols, and data sources. For example, Becker et al. (29) published U.S. DRLs for SPECT MPI using 7,311 studies from the American College of Radiology accreditation data. Ninety-five percent of cases in their study were rest-stress protocols. Rest-stress protocols also comprised 93% of North American cases in our study, but they represented only 46% of cases worldwide. In recent years, several U.S. reports have demonstrated comparable diagnostic performance and significant reductions in patient radiation exposure using "stress-first" imaging, whereby a normal stress study may obviate the need for subsequent rest imaging (31-35). The American Society of Nuclear Cardiology published updated guidelines in 2018 (24) that strongly recommended the use of stress-first imaging where feasible. Our data revealed that stress-first or stress-only protocols were used in just 7% of North American studies compared with 85% of European studies.

Additionally, we observed that reference levels for stress-only studies tended to fall between DRLs for the first dose of 1-day and multiday Tc-99m studies. For instance, the regional DRL for North American stress-only protocols was 18.8 mCi (696 MBq) versus 11.0 mCi (407 MBq) for the first dose of 1-day Tc-99m

TABLE 4 Worldwide and Regional AAAs for SPECT MPI From the INCAPS Registry

Protocol	Dose	Administered Activity, mCi (MBq)						
		Africa	Asia	Europe	Latin America	North America	Oceania	Worldwide
Tc-99m rest-stress or stress-rest, 1 day	1st	10.0 (370)	10.0 (370)	9.3 (344)	11.0 (407)	10.5 (389)	8.6 (318)	10.1 (374)
	2nd	17.0 (629)	27.8 (1,029)	19.2 (710)	30.0 (1,110)	31.8 (1,178)	27.0 (1,000)	28.0 (1,036)
Tc-99m rest-stress or stress-rest, 2 days	1st	25.0 (925)	21.0 (777)	16.2 (600)	20.0 (740)	30.9 (1,143)	21.9 (810)	17.8 (657)
	2nd	26.0 (962)	21.0 (777)	16.3 (603)	20.0 (740)	31.1 (1,151)	24.1 (892)	18.7 (690)
Tc-99m stress-only	1st	10.0 (370)	12.5 (463)	12.9 (477)	20.0 (740)	15.3 (566)	7.2 (265)	12.5 (463)
Tl-201, 1 injection	1st	–	3.1 (114)	2.8 (104)	4.0 (148)	–	2.0 (74)	3.0 (111)
Tl-201, 2 injections	1st	–	2.9 (106)	2.2 (81)	3.0 (111)	–	1.5 (55)	2.5 (93)
	2nd	–	1.1 (40)	1.1 (40)	1.0 (37)	–	0.5 (19)	1.0 (38)
Dual isotope	1st	–	3.0 (111)	3.5 (128)	3.0 (111)	3.0 (111)	2.0 (75)	3.0 (111)
	2nd	–	21.0 (777)	21.6 (800)	20.0 (740)	30.5 (1,129)	13.2 (490)	21.5 (796)

AAA = achievable administered activity; other abbreviations as in Tables 1 to 3.

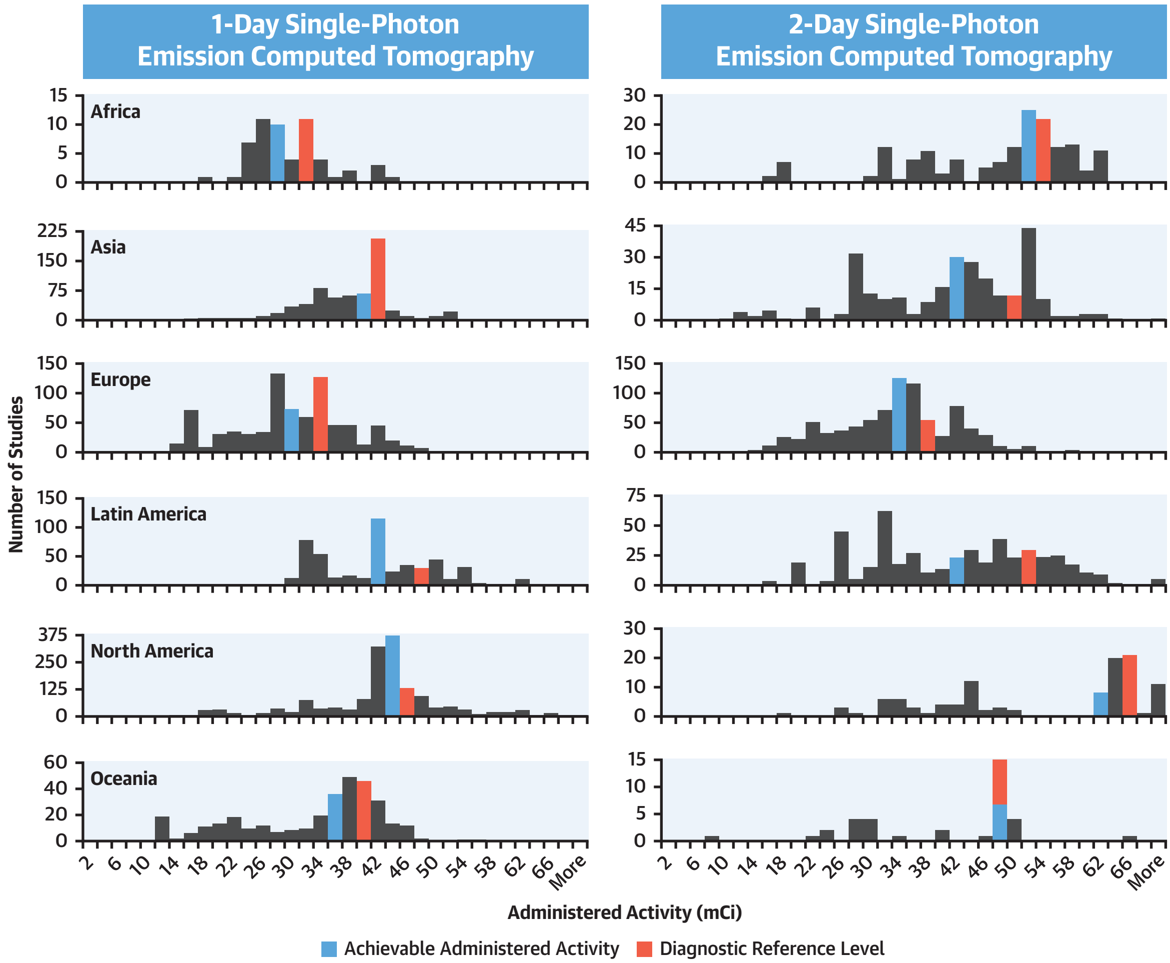
stress-rest protocols and 32.4 mCi (1,199 MBq) for the first dose of multiday protocols. This difference is likely due to the fact that stress-only protocols resemble a combination of both low-dose and high-dose initial stress studies. This finding was consistent across almost every region. In light of recent evidence and guidelines, it would be desirable for more North American laboratories to shift toward stress-first imaging, and differentiating DRLs by protocol sequence could help to further standardize international reporting and facilitate comparability of DRLs between regions.

Different methods of calculating and reporting DRLs may also affect the interpretation of variation between reports. National Council on Radiation Protection and Measurements report 172 (7) lists U.S. reference levels for SPECT MPI based on a 2010 survey where facilities were asked to report the minimum and maximum administered activities for various study protocols. This report uses the term "reference level" rather than DRL for non-x-ray examinations, including nuclear medicine. Reference levels are listed for the 75th percentile of the distribution of minimum activities and the 75th percentile of the distribution of maximum activities for each protocol, resulting in a wide range of values that is difficult to compare with existing data. For example, the reference levels for rest-stress Tc-99m-sestamibi studies were 14 to 31 mCi (rest) and 26 to 39 mCi (stress) (7). The lower end of the rest dose reference level range (i.e., 14 mCi) is greater than the DRL of 11 mCi from our data and 11.5 mCi reported in Becker et al. (29). This difference may be due to the fact that DRLs were not reported separately for 1-day and multiday protocols. We found that DRLs for 1-day Tc-99m studies were lower than DRLs for multiday studies in every region. Alessio et al. (22) point out that artificially inflated DRLs would allow laboratories to fall below the 75th percentile, and these labs would otherwise benefit from closer examination for radiation improvement strategies.

Similarly, European MPI data, published by the European Commission in report 180 (8), are limited to only 3 DRLs (Tl-201, Tc-99m tetrofosmin, and Tc-99m sestamibi). They report a 5-fold difference between the minimum and maximum DRL range for Tc-99m studies alone (300 to 1500 MBq). The investigators comment that the comparison of DRLs for myocardial perfusion studies was especially difficult due to differences in the reporting of protocols between European countries. Through a standardized worldwide dataset, INCAPS has enabled more granular, protocol-specific analyses and comparisons of regional DRLs. Researchers and organizations reporting DRLs should continue to focus on establishing standardized calculation and reporting methods to improve the comparability and clinical utility of regional DRLs.

STUDY LIMITATIONS. We acknowledge that this study is not without limitations. First, regional participation in INCAPS was variable, and the extent to which the facilities that participated in INCAPS are representative of all cardiac nuclear imaging centers in each region is unknown. Despite this, INCAPS is among the largest worldwide registries of SPECT MPI data, and it is the first regional data registry in Asia, Africa, and South America, serving as a baseline to compare future studies. Relatedly, voluntary participation in INCAPS raises the potential for volunteer bias (e.g., laboratories with higher doses or worse adherence to best practices may have been less inclined to participate), which might cause DRLs to be underestimated in some cases. However, where comparable, DRLs were generally in agreement with previously published data (29). Laboratories also submitted data during a limited time period that may not precisely reflect the variety and distribution of

CENTRAL ILLUSTRATION Regional Distributions of Administered Activities for Tc-99m Rest-Stress or Stress-Rest SPECT MPI Studies



Hirschfeld, C.B. et al. J Am Coll Cardiol Img. 2021;14(3):657–65.

Histograms showing the distribution of administered activities for 1-day **(left)** and 2-day **(right)** technetium Tc 99m (Tc-99m) stress-rest or rest-stress single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) studies for each world region. Each **bar** on the histogram represents a range of 2 mCi. The regional achievable administered activity (AAA) falls within the **blue bar** and the regional diagnostic reference level (DRL) falls within the **red bar**.

scans being performed in each facility, although, this is likely offset by sampling multiple centers in each region.

We also recognize that since the collection of INCAPS data, which was carried out in 2013, changes in hardware, software, clinical protocols, and legislation (35) have occurred that could influence DRLs. In general, advancements in technology have been shown to reduce patient radiation exposure. For example, laboratories using newer solid-state cadmium-zinc-telluride cameras can achieve a 50% reduction in administered activity using protocols specified in the 2016 American Society of Nuclear Cardiology Stress Protocols and Tracers guidelines (36). The use of advanced post-processing software could also enable facilities to perform stress-first studies with adequate image quality using administered activities of just 5 mCi on conventional sodium-iodide cameras (37). Previous INCAPS reports showed that camera-based dose-reduction strategies, including use of either attenuation correction, multiple positions, newer technology cameras, or advanced post-processing software were reported in just 27% of facilities worldwide (15). Hence, DRLs could be lower in regions with expanded implementation of advanced technologies. Because DRLs reported in this study may not completely reflect current regional practices, additional data are needed to better understand regional trends in use of these dose-optimizing practices and protocols and their impact on DRLs. In view of this, the IAEA will conduct a follow-up study, INCAPS II, now tentatively planned for 2021, which is expected to provide updated data on global and regional DRLs and AAAs for SPECT MPI.

CONCLUSIONS

INCAPS offers a unique opportunity to establish DRLs from a worldwide registry dedicated to MPI, enabling the first multiregional comparison of DRLs from a single standardized dataset. We observed significant variations in protocols, data collection methods, and analyses between regional studies and guidelines, which affected how DRLs were calculated and reported and made inter-regional comparisons of DRLs more challenging. INCAPS ameliorates some of these barriers by standardizing the analysis and reporting of regional data, enabling us to report more granular, protocol-specific details that are consistent between regions. As a cross-sectional analysis of actual patients' scans, the dataset may also be more representative of the variety, distribution, and frequency of scans seen in the clinical setting. The IAEA and partners are actively working on the next iteration of INCAPS enabling DRLs to be re-evaluated longitudinally. Worldwide and regional DRLs may be useful in establishing or revising guidelines or simply comparing laboratory protocols to regional trends. Efforts to reduce radiation exposure in SPECT MPI should continue through standardization of protocols and adherence to best practices.

ACKNOWLEDGMENTS The authors are grateful to the INCAPS Investigators Group (Supplemental Appendix) and their institutions for efforts in collecting the data, as well as the cooperating professional societies, including the American Society of Nuclear Cardiology, the Asian Regional Cooperative Council for Nuclear Medicine, Australian and New Zealand Society of Nuclear Medicine, British Nuclear Medicine Society/British Nuclear Cardiology Society, Comissão Nacional de Energia Nuclear, European Association of Nuclear Medicine, European Council of Nuclear Cardiology, IAEA, and the Intersocietal Accreditation Commission.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr. Einstein's institution has received funding for other research from Canon Medical Systems USA, Roche Medical Systems, and W. L. Gore & Associates; and he has served as a consultant to W. L. Gore & Associates. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Andrew J. Einstein, Columbia University Irving Medical Center, Seymour, Paul, and Gloria Milstein Division of Cardiology, 622 West 168th Street PH 10-203, New York, New York 10032, USA. E-mail: andrew.einstein@columbia.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This report constitutes the first multiregional report of reference levels for SPECT MPI, which may aid in the evaluation of international practice trends and the optimization of future clinical guidelines to further reduce population radiation exposure.

TRANSLATIONAL OUTLOOK: By using a single international registry, the analysis and reporting of regional reference levels can be more easily standardized, improving their comparability both at present and longitudinally in potential future studies.

REFERENCES

1. Fazel R, Krumholz HM, Wang Y, et al. Exposure to low-dose ionizing radiation from medical imaging procedures. N Engl J Med 2009;361:849–57.

2. Al Badarin FJ, Malhotra S. Diagnosis and prognosis of coronary artery disease with SPECT and PET. Curr Cardiol Rep 2019;21:57.

3. Einstein AJ. Effects of radiation exposure from cardiac imaging: how good are the data? J Am Coll Cardiol 2012;59:553–65.

4. Einstein AJ, Tilkemeier P, Fazel R, Rakotoarivelo H, Shaw LJ. American Society of Nuclear Cardiology. Radiation safety in nuclear cardiology-current knowledge and practice: results from the 2011 American Society of Nuclear Cardiology member survey. JAMA Intern Med 2013;173:1021–3.

5. Dorbala S, Blankstein R, Skali H, et al. Approaches to reducing radiation dose from radionuclide myocardial perfusion imaging. J Nucl Med 2015;56:592–9.

6. Shaw LJ, Marwick TH, Zoghbi WA, et al. Why all the focus on cardiac imaging? J Am Coll Cardiol Img 2010;3:789–94.

7. National Council on Radiation Protection and Measurements. Reference Levels and Achievable Doses in Medical and dental imaging: Recommendations for the United States. NCRP Report No. 172. Bethesda, MD: National Council on Radiation Protection and Measurements; 2012.

8. European Commission. Radiation Protection No. 180. Diagnostic Reference Levels in Thirty-Six European Countries: Part 2/2; 2020. Available at: https://ec.europa.eu/energy/sites/ener/files/documents/RP180%20part2.pdf. Accessed January 9, 2020.

9. American College of Radiology. ACR–AAPM Practice Parameter for Reference Levels and Achievable Administered Activity for Nuclear Medicine and Molecular Imaging. Resolution 53. 2015 2015. Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/reflevels-nucmed.pdf?la=en. Accessed December 10, 2019.

10. Cerqueira MD, Allman KC, Ficaro EP, et al. Recommendations for reducing radiation exposure in myocardial perfusion imaging. J Nucl Cardiol 2010;17:709–18.

11. Dorbala S, Di Carli MF, Delbeke D, et al. SNMMI/ASNC/SCCT guideline for cardiac SPECT/CT and PET/CT 1.0. J Nucl Med 2013;54:1485–507.

12. Fazel R, Dilsizian V, Einstein AJ, Ficaro EP, Henzlova M, Shaw LJ. Strategies for defining an optimal risk-benefit ratio for stress myocardial perfusion SPECT. J Nucl Cardiol 2011;18:385–92.

13. Field S, Arthur RJ, Coakley AJ, et al. Guidelines on Patient Dose to Promote the Optimisation of Protection for Diagnostic Medical Exposures: Report of an Advisory Group on Ionising Radiation. Chilton, UK: National Radiological Protection Board; 1999.

14. Hirshfeld JW Jr., Ferrari VA, Bengel FM, et al. 2018 ACC/HRS/NASCI/SCAI/SCCT Expert consensus document on optimal use of ionizing radiation in cardiovascular imaging: best practices for safety and effectiveness: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol 2018;71:e283–351.

15. Einstein AJ, Pascual TN, Mercuri M, et al., for the INCAPS Investigators Group. Current worldwide nuclear cardiology practices and radiation exposure: results from the 65 country IAEA Nuclear Cardiology Protocols Cross-Sectional Study (INCAPS). Eur Heart J 2015;36:1689–96.

16. Jerome SD, Tilkemeier PL, Farrell MB, Shaw LJ. Nationwide laboratory adherence to myocardial perfusion imaging radiation dose reduction practices: a report from the Intersocietal Accreditation Commission Data Repository. J Am Coll Cardiol Img 2015;8:1170–6.

17. ICRP. 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. Oxford, UK: Pergamon Press; 1991.

18. ICRP. Radiological Protection and Safety in Medicine. ICRP Publication 73. Oxford, UK: Pergamon Press; 1996.

19. Vano E, Miller DL, Martin CJ, et al. for the ICRP. ICRP publication 135: diagnostic reference levels in medical imaging. Ann ICRP 2017;46:1–144.

20. Diagnostic reference levels in medical imaging: review and additional advice. Ann ICRP 2001;31:33–52.

21. Vassileva J, Rehani M. Diagnostic reference levels. AJR Am J Roentgenol 2015;204:W1–3.

22. Alessio AM, Farrell MB, Fahey FH. Role of reference levels in nuclear medicine: a report of the SNMMI Dose Optimization Task Force. J Nucl Med 2015;56:1960–4.

23. American College of Radiology. Practice guidelines and technical standards. Reston, VA: American College of Radiology; 2008; p 799–804.

24. Dorbala S, Ananthasubramaniam K, Armstrong IS, et al. Single photon emission computed tomography (SPECT) myocardial perfusion imaging guidelines: instrumentation, acquisition, processing, and interpretation. J Nucl Cardiol 2018;25:1784–846.

25. McCollough C, Branham T, Herlihy V, et al. Diagnostic reference levels from the ACR CT Accreditation Program. J Am Coll Radiol 2011;8:795–803.

26. European Commission, Food and Agriculture Organization of the United Nations, International Atomic Energy Agency, et al. Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards. IAEA Safety Standards Series No. GSR Part 3. Vienna, Austria: IAEA; 2014.

27. International Atomic Energy Agency. Radiation Protection and Safety in Medical Uses of Ionizing Radiation. IAEA Safety Standards Series No. SSG-46. Vienna, Austria: IAEA; 2018.

28. Alkhybari EM, McEntee MF, Brennan PC, Willowson KP, Hogg P, Kench PL. Determining and updating PET/CT and SPECT/CT diagnostic reference levels: a systematic review. Radiat Prot Dosimetry 2018;182:532–45.

29. Becker MD, Butler PF, Bhargavan-Chatfield M, et al. Adult gamma camera myocardial perfusion imaging: diagnostic reference levels and achievable administered activities derived from ACR Accreditation Data. J Am Coll Radiol 2016;13:688–95.

30. Australian Radiation Protection and Nuclear Safety Agency. Nuclear Medicine Diagnostic Reference Levels (DRLs). 2017 2017. Available at: https://www.arpansa.gov.au/sites/default/files/nuclear-medicine-diagnostic-reference-levels.pdf. Accessed February 2, 2020.

31. Chang SM, Nabi F, Xu J, Raza U, Mahmarian JJ. Normal stress-only versus standard stress/rest myocardial perfusion imaging: similar patient mortality with reduced radiation exposure. J Am Coll Cardiol 2010;55:221–30.

32. Duvall WL, Wijetunga MN, Klein TM, et al. The prognosis of a normal stress-only Tc-99m myocardial perfusion imaging study. J Nucl Cardiol 2010;17:370–7.

33. Einstein AJ, Johnson LL, DeLuca AJ, et al. Radiation dose and prognosis of ultra-low-dose stress-first myocardial perfusion SPECT in patients with chest pain using a high-efficiency camera. J Nucl Med 2015;56:545–51.

34. Perrin M, Djaballah W, Moulin F, et al. Stress-first protocol for myocardial perfusion SPECT imaging with semiconductor cameras: high diagnostic performances with significant reduction in patient radiation doses. Eur J Nucl Med Mol Imaging 2015;42:1004–11.

35. Council of the European Union. II (Non-legislative acts): Directives: Council Directive 2013/59/Euratom of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation and repealing directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43 Euratom and 2003/122/Euratom. Off J Eur Union 2014;L13:1–73.

36. Henzlova MJ, Duvall WL, Einstein AJ, Travin MI, Verberne HJ. ASNC imaging guidelines for SPECT nuclear cardiology procedures: stress, protocols, and tracers. J Nucl Cardiol 2016;23:606–39.

37. DePuey EG, Ata P, Wray R, Friedman M. Very low-activity stress/high-activity rest, single-day myocardial perfusion SPECT with a conventional sodium iodide camera and wide beam reconstruction processing. J Nucl Cardiol 2012;19:931–44.

KEY WORDS administered activity, diagnostic reference level, radiation dose reduction, SPECT myocardial perfusion imaging

APPENDIX For the list of INCAPS Investigators and supplemental tables, please see the online version of this paper.