



What is Research-Grade RWE and Why Does it Matter?

Global themes for regulators for assessing quality, fit-for-purpose and audit trails

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RWE retracted 4 weeks after publication, citing lack of data access to 3rd party auditor

This article has been retracted: N Engl J Med. DOI: 10.1056/NEJMc2021225.
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19

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ABSTRACT

BACKGROUND

Coronavirus disease 2019 (Covid-19) may disproportionately affect people with cardiovascular disease. Concern has been aroused regarding a potential harmful effect of angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) in this clinical context.

METHODS

Using an observational database from 169 hospitals in Asia, Europe, and North America, we evaluated the relationship of cardiovascular disease and drug therapy with in-hospital death among hospitalized patients with Covid-19 who were admitted between December 20, 2019, and March 15, 2020, and were recorded in the Surgical Outcomes Collaborative registry as having either died in the hospital or survived to discharge as of March 28, 2020.

RESULTS

Of the 8910 patients with Covid-19 for whom discharge status was available at the time of the analysis, a total of 515 died in the hospital (5.8%) and 8395 survived to discharge. The factors we found to be independently associated with an increased risk of in-hospital death were an age greater than 65 years (mortality of 10.0%, vs. 4.9% among those ≤ 65 years of age; odds ratio, 1.93; 95% confidence interval [CI], 1.60 to 2.41), coronary artery disease (10.2%, vs. 5.2% among those without disease; odds ratio, 2.70; 95% CI, 2.08 to 3.51), heart failure (15.3%, vs. 5.6% among those without heart failure; odds ratio, 2.48; 95% CI, 1.62 to 3.79), cardiac arrhythmia (11.5%, vs. 5.6% among those without arrhythmia; odds ratio, 1.95; 95% CI, 1.33 to 2.86), chronic obstructive pulmonary disease (14.2%, vs. 5.6% among those without disease; odds ratio, 2.96; 95% CI, 2.00 to 4.40), and current smoking (9.4%, vs. 5.6% among former smokers or nonsmokers; odds ratio, 1.79; 95% CI, 1.29 to 2.47). No increased risk of in-hospital death was found to be associated with the use of ACE inhibitors (2.1% vs. 6.1%; odds ratio, 0.33; 95% CI, 0.20 to 0.54) or the use of ARBs (6.8% vs. 5.7%; odds ratio, 1.25; 95% CI, 0.87 to 1.74).

CONCLUSIONS

Our study confirmed previous observations suggesting that underlying cardiovascular disease is associated with an increased risk of in-hospital death among patients hospitalized with Covid-19. Our results did not confirm previous concerns regarding a potential harmful association of ACE inhibitors or ARBs with in-hospital death in this clinical context. (Funded by the William Harvey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women's Hospital.)

METHODS

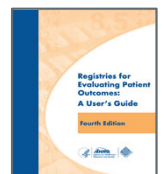
DATA SOURCE

We analyzed deidentified data from the Surgical Outcomes Collaborative (Surgisphere), an international registry. Our analysis included data from 169 hospitals located in 11 countries in Asia, Europe, and North America. The collaborative uses automated extraction of data from inpatient and outpatient electronic health records, supply-chain databases, and financial records, combined with point-of-care data entry for procedures. A manual data-entry process is used for quality assurance and validation. Data are collected through automated data transfers that capture information from each health care entity at regular intervals on a prospective, ongoing basis. Verifiable source documentation for the data elements includes electronic inpatient and outpatient medical records.

Data acquisition is facilitated through the use of a standardized Health Level Seven-compliant data dictionary. After this data dictionary is harmonized with data from electronic health records, the majority of the data acquisition is completed with automated interfaces. The collected data sample from each health care entity is validated against financial records and external databases. All protected health information is stripped from each record before storage in a cloud-based data warehouse. The collaborative is compliant with the Agency for Healthcare Research and Quality guidelines for registries and the Food and Drug Administration guidance on real-world evidence. The collection and analysis of data in the registry have been deemed exempt from ethics review.























Unknown international registry publishes ground-breaking COVID research

- Speed record: 6 weeks from end of patient accrual to publication
- Manual validation of EMR data in 169 hospitals and ~96,000 people? [How?](#)
- Data validated against financial records and external databases? [How?](#)
- Claims compliance with AHRQ registry guidelines? [I think not](#)



Available at
<https://effectivehealthcare.ahrq.gov>

Even without formal guidance, RWE is helping to shape some regulatory decisions

			FDA		EMA		NMPA	
			Approval	Label Expansion	Conditional Approval	Approval	Label Expansion	
Pragmatic		 INVEGA SUSTENNA® paliperidone palmitate 39mg, 78mg, 117mg, 156mg, 234mg	Schizophrenia		(2018)			
External Comparators		 BAVENCIO® avelumab 20 mg/mL	Metastatic Merkel cell carcinoma	(2017) Accelerated		(2017)		
		 Brineura® (cerliponase alfa)	Infantile batten disease	(2017)			(2017)	
	 	 YESCARTA® (axicabtagene ciloleuce)	Diffuse large B-cell lymphoma	(2017)				(2018)
		 KYMRIAH™ (tisagenlecleucel) Suspension for IV infusion	Diffuse large B-cell lymphoma					(2018)
		Omegaven	Parenteral nutrition-associated cholestasis	(2018)				
		 BLINCYTO® (blinatumomab) Injection 90mcg/0.5mL	B-cell precursor acute lymphoblastic leukemia in 1 st /2 nd complete remission with MRD ≥ 0.1%		(2018)			(2019)
		 MONJUVI® tislelizumab-Cxix 200mg for injection, 100 mg/mL	Diffuse large B-cell lymphoma	(2020)				
Observational		 LUTATHERA® (¹⁷⁷ Lu-DOTA-TATE) Injection	SSTR-positive (GEP-NETs)	(2018)				(2017)
	 A Member of the Roche Group	 AVASTIN® bevacizumab	Metastatic or recurrent squamous NSCLC in combination with platinum-based chemotherapy					(2018)
		 IBRANCE® exemestane	HR+, HER2- advanced/metastatic breast cancer in males		(2019)			

MRD = minimal residual disease; SSTR = Somatostatin receptor; GEP-NETs = gastroenteropancreatic; neuroendocrine tumors; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor

Regulatory Market Trends

April 2019: HealthCanada worked to **optimize the use of RWE** for regulatory decisions

June 2020: Health Canada developing a plan to **optimize use of RWE** into regulatory and reimbursement decisions



October 20: MHRA launches public consultation to review **external comparators guidance**



April 2020: EC **Medical Device Regulation** 2017/745 (the "MDR") new effective date May 2021 requires post market follow-up



Sep 2020: Japanese MHLW Drafts Guidelines for **Use of Patient Registry Data in Regulatory Filing** (final Mar 2021)



May 2019: FDA guidance to **encourage sponsors to provide details on RWD** used as part of regulatory submissions

September/October 2020: FDA webcast on **use of RWE to address COVID**



January 2020: EMA-HMA big data task force published **prioritised 10 recommendations**

September 2020: EMA-HMA published its workplan aims to **increase the utility of big data in regulation**

December 2020: Public **consultation** on big data



January and August 2020: Chinese Center for Drug Evaluation **released guidance for RWE to use** to support drug development








March 2019: The Central Drugs Standard Control Organization provide **guidance on the conduct of observational or non-interventional study**



Note: Selected publications, not exhaustive

Common regulatory themes

Expectations for High-Quality Real World Data

Reliability and Quality Criteria		 Health Canada	 <small>EUROPEAN MEDICINES AGENCY SCIENCE · MEDICINES · HEALTH</small>	 (Japan)	 <small>NATIONAL MEDICAL PRODUCTS ADMINISTRATION 国家药品监督管理局</small> (China)
Accuracy	✓				
Completeness	✓		✓	✓	✓
Consistency	✓		✓	✓	✓
Relevance		✓	✓	✓	
Traceability		✓			
Transparency		✓	✓		✓

FDA framework for evaluating RWD/RWE



- Are the RWD are fit for study purpose?
- Is the trial or study design likely to provide adequate scientific evidence to answer or help answer the regulatory question?
- Does the study conduct meets FDA regulatory requirements?

Contact information



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