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MINIREVIEWS

Seeing through the myths: Practical aspects of diagnostic point-of-care ultrasound in nephrology

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Abstract

Point of care ultrasonography (POCUS) is emerging as an invaluable tool for guiding patient care at the bedside, providing real-time diagnostic information to clinicians. Today, POCUS is recognized as the fifth pillar of bedside clinical examination, alongside inspection, palpation, percussion, and auscultation. In spite of growing interest, the adoption of diagnostic POCUS in nephrology remains limited, and comprehensive training beyond kidney ultrasound is offered in only a few fellowship programs. Moreover, several misconceptions and barriers surround the integration of POCUS into day-to-day nephrology practice. These include myths about its scope, utility, impact on patient outcomes and legal implications. In this minireview, we address some of these issues to encourage wider and proper utilization of POCUS.

Key Words: Ultrasound; Point of care ultrasonography; Doppler; Congestion; Hemodynamics; Nephrology

Core Tip: Nephrologists frequently encounter challenges in assessing fluid volume status in their daily practice, and point of care ultrasonography (POCUS) can significantly enhance the sensitivity of traditional physical examination in such scenarios. Not only does POCUS aid in swift diagnosis, but it also reduces fragmentation of care. While it may obviate the need for additional imaging studies in specific cases, it should not be considered a replacement for comprehensive consultative imaging. The effectiveness of POCUS largely relies on the proficiency and experience of the operator, which, in turn, is influenced by the quality of training provided.

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INTRODUCTION

Point of care ultrasonography (POCUS) is a focused ultrasound examination performed by the treating clinician at the bedside to address specific questions that aid in guiding patient management[1]. Ultrasonography itself has been a trusted imaging modality for several decades. During the 1980s, the development of real-time ultrasound revolutionized the way sonographic images were viewed, eliminating any lag between signal generation and image display. This breakthrough created new opportunities for physicians to perform bedside ultrasound evaluations of trauma patients in emergency settings, leading to the evolution of the POCUS we recognize today[2]. With ongoing technological advancements and the miniaturization of ultrasound devices, POCUS has gained significant momentum in the recent past emerging as the fifth pillar of physical examination alongside traditional four pillars, namely inspection, palpation, percussion, and auscultation. As such, it is being incorporated into medical school curricula. According to a 2019 survey, over 70% of the responding medical schools in the United States reported having a formal POCUS curriculum. Interestingly, 73.8% of these schools have integrated POCUS into basic science courses, highlighting its role in establishing a strong foundation in anatomy and physiology before entering the clinical years[3]. Despite growing interest, the adoption of diagnostic POCUS in nephrology remains sparse and comprehensive training beyond kidney ultrasound is only offered by a few select fellowship programs[4]. This has two significant implications for the near future. Firstly, prospective nephrology fellows who already received basic POCUS training and anticipate learning specialty-specific POCUS applications during their fellowship are left disappointed. This negatively impacts the already dwindling interest in nephrology as a career choice. Secondly, when fellows with some POCUS training use it during rounds, it can create confusion in the clinical decision-making process if the supervising physicians are unfamiliar with the findings. In addition to the lack of trained faculty, several misconceptions surrounding the use of POCUS hinder its widespread adoption. In this minireview, we aim to dispel common myths associated with integrating POCUS into day-to-day nephrology practice.

Myth: Pocus is the same as a comprehensive ultrasound study performed by the radiology department

POCUS constitutes limited ultrasound examinations performed by the clinician at the patient's bedside, with the specific purpose of answering "focused questions" to confirm a suspected diagnosis or narrow down the differential. Examples of such questions include, "Does this patient with acute kidney injury (AKI) have hydronephrosis?", "Does this patient with intra-dialytic hypotension have pericardial effusion?", or "Is this location of arteriovenous fistula suitable for cannulation?". On the other hand, comprehensive referral ultrasound studies performed by the radiology or cardiology departments involve a thorough assessment of an anatomical region, documenting predefined parameters and measurements. In addition, POCUS reduces fragmentation of care by allowing multiple evaluations performed during the same study. For example, a nephrologist evaluating a patient with suspected congestive nephropathy can assess cardiac function, right atrial pressure, presence or absence of venous congestion, pleural effusion, and ascites in a few minutes at bedside[5,6]. In contrast, without POCUS, obtaining answers to the same questions would require ordering a multitude of studies, including an echocardiogram, a chest radiograph, an abdominal sonogram, and a duplex study of the right upper quadrant and kidney. This process would consume significant time and resources, more so when repeating an entire study to follow one or two imaging parameters (*e.g.*, improvement in Doppler stigmata of venous congestion). With that being said, POCUS users need to use their clinical judgement in order to decide when a focused examination would suffice and when a more extensive assessment may be necessary to make accurate and informed clinical decisions. For instance, while a nephrologist using POCUS might be able to detect mitral regurgitation as a potential cause for unilateral pulmonary edema, accurately grading the lesion and providing detailed information related to mitral valve surgery would be beyond their expertise. Likewise, while a POCUS user may suspect renal artery stenosis based on the intrarenal Doppler waveform, performing a comprehensive evaluation would be time-consuming and necessitates skill levels beyond typical POCUS training (Figure 1).

Myth: Pocus is unnecessary if we improve training in conventional physical examination skills

It is true that physical examination skills are declining among physicians[7,8]. However, a less acknowledged aspect is that the diagnostic accuracy of physical examination is limited[9-12]. The so-called 'classic' signs and symptoms were described in an era when late-stage presentations were common, often occurring after the onset of significant symptoms. As a result, there is a need for a more sensitive bedside tool to detect pathology earlier, before substantial organ damage has occurred, and to provide timely guidance for patient management. Therefore, it is essential not only to enhance the instruction of physical examination skills but also to augment them by incorporating POCUS. It is now well-established that POCUS significantly improves the sensitivity of physical examination. For instance, in a study including 32 patients with acute respiratory distress syndrome, lung ultrasound demonstrated a diagnostic accuracy of 93% for pleural effusion, 97% for alveolar consolidation, and 95% for alveolar-interstitial syndrome. In comparison, the accuracy of auscultation in detecting these abnormalities was much lower, at 61%, 36%, and 55%, respectively[13]. Similarly, in a study involving 926 critically ill patients admitted to the intensive care unit, it was observed that 51% of those with

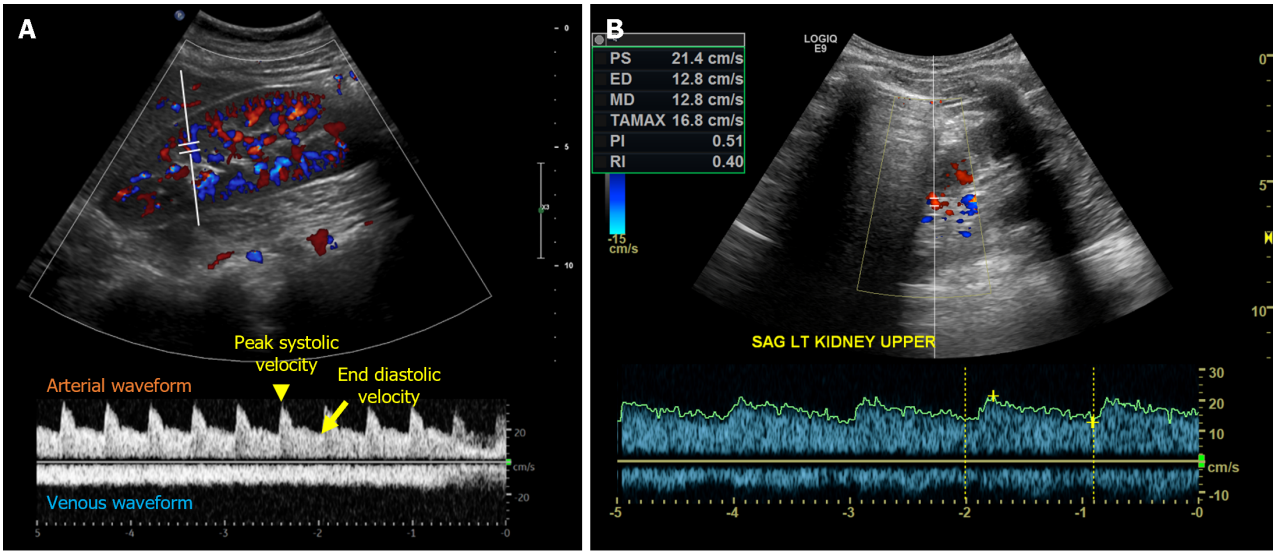

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Figure 1 Intrarenal Doppler. A and B: Intrarenal Doppler demonstrated normal waveforms (A), tardus parvus (B) waveform in a case of suspected renal artery stenosis that should warrant further investigations such as radiology-performed Doppler ultrasonography and/or magnetic resonance angiography. A and B: Citation: Batool A, Chaudhry S, Koratala A. Transcending boundaries: Unleashing the potential of multi-organ point-of-care ultrasound in acute kidney injury. *World J Nephrol* 2023; 12: 93-103. Copyright© The Authors 2023. Published by Baishideng Publishing Group Inc (corresponding author's prior open access publication).

pulmonary edema on lung POCUS showed normal findings on auscultation[14]. Moreover, the incorporation of POCUS has demonstrated significant improvements in diagnostic capabilities for common cardiac conditions[15-17]. These observations are very much relevant to nephrologists who frequently rely on physical examination to assess volume status and adjust ultrafiltration goals or diuretic therapy. Furthermore, certain applications such as ruling out obstructive uropathy or evaluating venous blood flow patterns to guide decongestive therapy, cannot be achieved through conventional examination methods regardless of clinicians' skill level. Figure 2 depicts a scenario in which a patient with heart failure and AKI received intravenous fluids under the assumption of overdiuresis, given the absence of pedal edema or shortness of breath. Nevertheless, POCUS revealed a dilated inferior vena cava and significantly pulsatile portal vein, indicating severe venous congestion. In response to these findings, intravenous diuretics were administered, leading to an improvement in serum creatinine levels.

Myth: The scope of nephrologist-performed pocus is confined to kidney ultrasound

The scope of POCUS depends on two main factors: Physician's competency and the relevance of a specific sonographic application to the physician's specialty. There is little debate about the relevance of kidney and urinary bladder ultrasound for nephrologists, as they are expected to diagnose structural abnormalities of the kidneys and integrate this information into clinical decision-making[18]. However, in real-life situations, consulting teams often order a formal renal sonogram before seeking nephrology input in cases of AKI. Therefore, while nephrologist-performed urinary tract POCUS can be beneficial, its utility is limited to specific scenarios, such as avoiding patients' referral to radiology to get an ultrasound in the outpatient setting or diagnosing Foley catheter obstruction in a patient with sudden decrease in urine output, among others. A significant portion of a nephrologist's time on a consultation service is devoted to managing patients with complex fluid and electrolyte disorders. Therefore, it is conceivable that the assessment of volume status using POCUS is vital in nephrology practice. As outlined in prior publications, incorporating multi-organ POCUS, which includes focused cardiac ultrasound, lung ultrasound, and Doppler assessment of systemic veins, greatly assists in evaluating cases of hemodynamic AKI[5,19,20]. This is especially valuable in addressing common diagnostic challenges such as hepatorenal dysfunction[21]. In addition, POCUS facilitates assessment of acute abnormalities of arteriovenous access in the dialysis unit and thereby guides appropriate management. Figure 3 outlines the sonographic applications commonly used in nephrology practice. The next question is whether nephrologists are permitted to perform multi-organ POCUS. The answer is yes. In 1999, the American Medical Association House of Delegates passed a resolution (H-230.960; reaffirmed 2020) stating that "ultrasound imaging is within the scope of practice of appropriately trained physicians"[22]. Additionally, each hospital's medical staff should review and approve criteria for granting ultrasound privileges, taking into account physicians' background and training in accordance with recommendations developed by their respective specialty societies. Hence it is clear that the ability to perform POCUS is not determined by the physician's specialty but rather by their training and competency. Currently, nephrologists have access to multiple certification opportunities tailored to their skill levels though development of specialty-specific universal competency standards remains a work in progress[23].

Myth: Pocus should be incorporated only if it enhances patient survival

POCUS is often criticized for the lack of robust data demonstrating its direct impact on mortality. However, it is essential

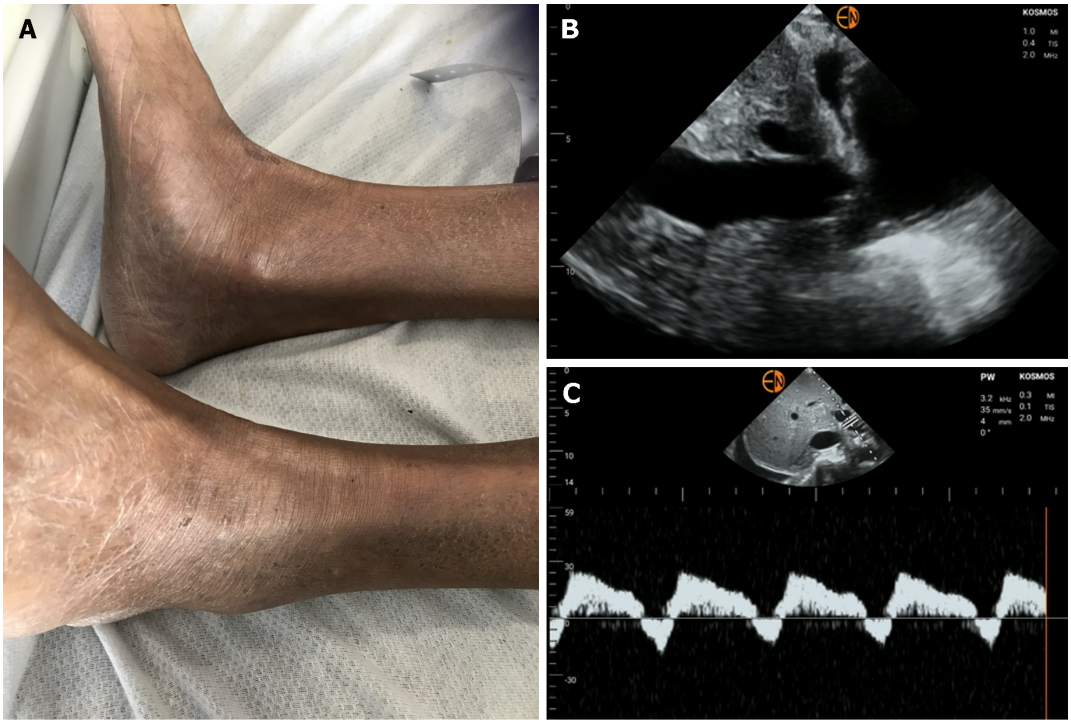

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Figure 2 A case of discrepant clinical and point of care ultrasonography findings. A: Absent pedal edema; B: Plethoric inferior vena cava suggestive of elevated right atrial pressure; C: Pulsatile portal vein Doppler with flow reversal indicative of severe venous congestion.

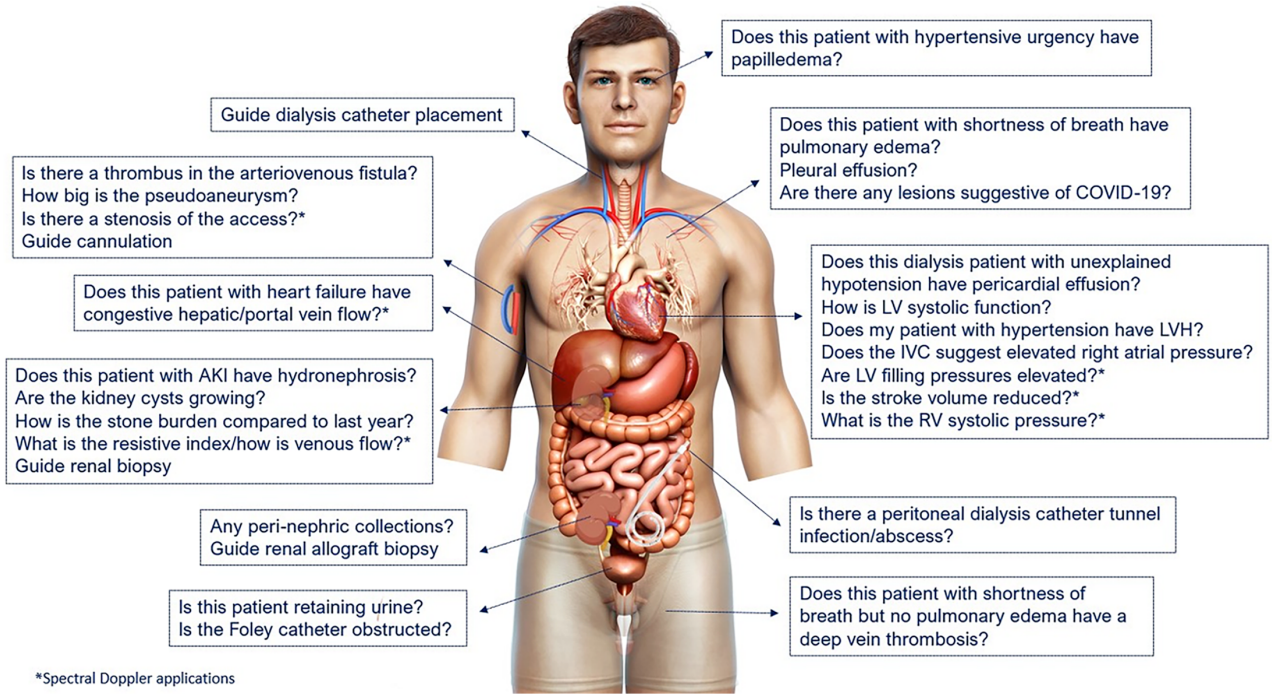

Figure 3 Scope of nephrology-related point of care ultrasonography: Organ-specific focused questions that can be answered by bedside ultrasonography. Those marked with asterisk (*) indicate advanced sonographic applications requiring a higher operator skill level/additional training. COVID-19: Coronavirus disease 2019; LV: Left ventricle; LVH: Left ventricular hypertrophy; IVC: Inferior vena cava; RV: Right ventricle. Citation: Koratala A, Reisinger N. POCUS for Nephrologists: Basic Principles and a General Approach. *Kidney360* 2021; 2: 1660-1668. Copyright © 2021 by the American Society of Nephrology. The authors have obtained the permission for figure using from the Wolters Kluwer Health, Inc (Supplementary material).

to remember that POCUS is a diagnostic aid. For a meaningful effect on mortality, it needs to be combined with treatments that have the ability to improve patient survival. As a diagnostic test, POCUS is expected to have better diagnostic accuracy compared to conventional methods, which it does as discussed above. Nevertheless, POCUS findings do have a significant impact on several clinically relevant and measurable outcomes such as time to diagnosis, need for imaging studies, healthcare cost burden, and patient satisfaction. For instance, in a systematic review and meta-analysis including 5393 patients with dyspnea, the time to correct diagnosis and treatment were significantly shorter in the POCUS group compared to those receiving conventional care (mean difference -63 min and -27 min respectively). Interestingly, patients in the POCUS group had significantly higher odds of receiving appropriate therapy *vs* controls (odds ratio = 2.31; 95% confidence interval: 1.61-3.32). Further, the length of stay in the intensive care unit was significantly shorter in the group managed using POCUS (mean difference -1.27 d)[24]. This clinical scenario is pertinent to nephrologists as they are often responsible for managing patients with dyspnea related to fluid overload. The ability to quickly differentiate between dyspnea caused by fluid accumulation and other potential causes is crucial in guiding appropriate interventions. Similarly, POCUS-guided management has shown to reduce the number of subsequent imaging studies including chest radiographs, echocardiograms and computed tomography scans thereby having a favorable impact on the healthcare costs[25,26]. Likewise, in hemodialysis patients, POCUS-guided titration of ultrafiltration has demonstrated more significant reductions in left ventricular filling pressures, cardiac chamber dimensions and ambulatory blood pressure readings, indicating an effective treatment approach[27,28]. With respect to patient-reported outcomes, there is increasing evidence that POCUS enhances patient satisfaction and facilitates better understanding of their diagnosis[29,30]. This is of particular interest to nephrologists, as they must adeptly communicate dietary restrictions and medication adherence to asymptomatic patients. In this context, discussing and presenting POCUS images to patients could prove effective[31]. The fundamental responsibility of a physician is to make accurate diagnoses through thoughtful integration of history and physical examination findings. It is illogical to forgo the use of improved bedside diagnostic tools merely because there may not be a treatment that directly impacts mortality.

Myth: Acquiring competency in pocus is a fast and simple process

POCUS comprises three essential components: Image acquisition, interpretation, and clinical integration. Competency in POCUS means being proficient in all these aspects. In medical school, students typically receive longitudinal instruction in physical examination, starting from the first year, progressing from normal findings to abnormal findings, and finally, correlating these findings clinically to arrive at a diagnosis and develop a management plan. As such, it is logical to assume that achieving competency in POCUS cannot be accomplished just by attending a short course. It requires persistent practice under the guidance of experts, if possible, or at the very least, cross-checking findings with the reports of formal imaging studies till the learner is consistently able to obtain images of acceptable quality and independently interpret them. The duration of training can vary significantly based on the specific sonographic applications and the level of expertise needed. For instance, mastering Doppler echocardiography takes considerably more time compared to learning how to obtain basic cardiac views. As expected, the literature documents highly variable training durations, ranging from 4-320 h according to a systematic review[32]. Merely attending training sessions does not ensure competence. It must be assessed through various methods, such as knowledge checks, objective structured clinical examinations, standardized direct observation tools and periodic quality assessments. In addition, a benchmark of a minimum number of scans to be performed is commonly used when determining certification criteria or granting hospital privileges for POCUS. For example, the American College of Emergency Physicians policy statement on emergency ultrasound recommends that a trainee should perform a minimum of 25-50 quality-reviewed ultrasounds per core application and a total of 150-300 scans as part of POCUS training[33]. These recommendations are widely adopted by hospital credentialing committees and other POCUS-performing specialties albeit with necessary modifications depending on the scope of practice. In nephrology, current expert recommendation includes a minimum of 25 quality-reviewed scans per basic application (*e.g.*, kidney, focused cardiac, lung, vascular access) and 50 per advanced application (*e.g.*, Doppler cardiac, systemic venous Doppler, arteriovenous fistula flow assessment)[34]. To summarize, mastering POCUS is a gradual and long-term process, and physicians should plan for a stepwise learning approach. Additionally, it is crucial to be aware of both personal limitations and the limitations of the equipment being used (*e.g.*, handheld ultrasound device *vs* a traditional portable machine) when interpreting the scans to avoid misdiagnosis or missing significant findings. All these factors must be taken into consideration when nephrology faculty are considering starting a POCUS training program at their institutions. Division leadership should acknowledge the significant time commitment involved and allocate the necessary resources to support the initiative. Figure 4 depicts essential elements for implementing a robust POCUS program within an institution.

Myth: Pocus has limited utility because of its operator-dependent nature

POCUS is frequently criticized for its operator-dependent nature, but this limitation is intrinsic to ultrasonography as an imaging method in general irrespective of who performs it (*e.g.*, a nephrologist or a professional sonographer or a radiologist). In contrast to other imaging modalities such as CT or magnetic resonance imaging with standardized image acquisition, obtaining optimal images relies on the expertise of the person performing ultrasound. Therefore, it is not a POCUS-specific (clinician-performed ultrasound) limitation. In reality, nearly every aspect of physician-patient interaction, such as history-taking, physical examination, and interpreting laboratory data, is operator-dependent. The emphasis should be on providing proper training to the operator rather than blaming the modality itself.

Myth: Incorporating pocus makes physicians more susceptible to lawsuits

The fear of misinterpreting findings or overlooking incidental findings, which could lead to adverse legal actions, is

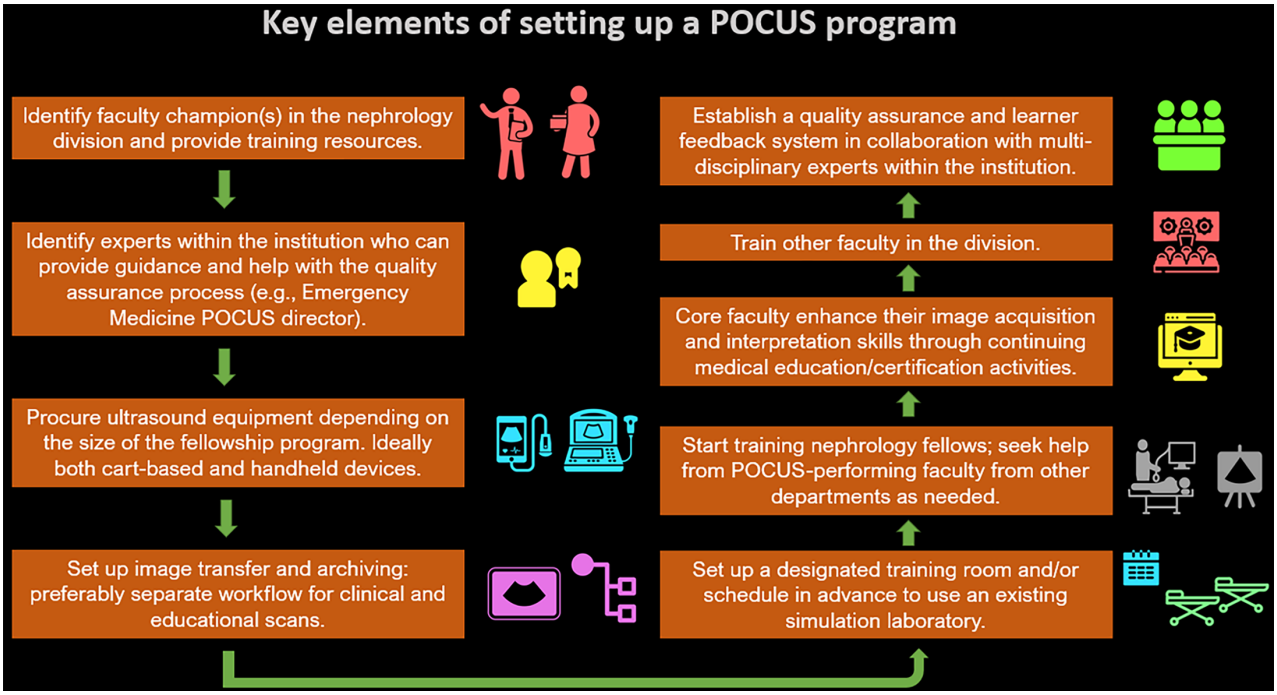

Figure 4 Flow chart depicting the key elements of establishing a point of care ultrasonography program at the institutional level. POCUS: Point of care ultrasonography. Citation: Koratala A, Reisinger N. POCUS for Nephrologists: Basic Principles and a General Approach. *Kidney360* 2021; 2: 1660-1668. Copyright © 2021 by the American Society of Nephrology. The authors have obtained the permission for figure using from the Wolters Kluwer Health, Inc (Supplementary material).

frequently seen as a hindrance to the adoption of POCUS in nephrology practice[35]. Several studies have examined lawsuits involving POCUS performed by various specialties. However, to date, no study has indicated that missed findings on focused or limited ultrasound scans resulted in adverse legal action against physicians. Instead, the research suggests that adverse legal action is more commonly associated with failure to perform POCUS in a timely manner when required[36-40]. In this context, implementing a hospital wide system for archiving POCUS images and standardizing the reporting of findings can be beneficial. Such a system streamlines the process of providing timely feedback to trainees, facilitates billing procedures, and allows for seeking expert opinion when uncertainty arises.

CONCLUSION

In conclusion, POCUS serves as a valuable addition to nephrologists' toolkit, enhancing bedside diagnosis. However, it is essential to remember that no matter how advanced the technology is, it cannot replace astute clinical judgment and the appropriate integration of clinical information. This rule applies to POCUS as well, because any oversight in attention to details, improper technique, or misinterpretation of findings may lead to inappropriate patient management. As such, professional organizations should collaborate in developing guidelines for training and accreditation processes. Future studies should focus on assessing the impact of structured longitudinal curricula on learners' competency and establishing protocols for the optimal use of POCUS in various nephrology-related clinical scenarios.

FOOTNOTES

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REFERENCES

1 **Díaz-Gómez JL**, Mayo PH, Koenig SJ. Point-of-Care Ultrasonography. *N Engl J Med* 2021; **385**: 1593-1602 [PMID: 34670045 DOI: 10.1056/NEJMra1916062]
2 **Kendall JL**, Hoffenberg SR, Smith RS. History of emergency and critical care ultrasound: the evolution of a new imaging paradigm. *Crit Care Med* 2007; **35**: S126-S130 [PMID: 17446770 DOI: 10.1097/01.CCM.0000260623.38982.83]
3 **Nicholas E**, Ly AA, Prince AM, Klawitter PF, Gaskin K, Prince LA. The Current Status of Ultrasound Education in United States Medical Schools. *J Ultrasound Med* 2021; **40**: 2459-2465 [PMID: 33448471 DOI: 10.1002/jum.15633]
4 **Koratala A**, Olaoye OA, Bhasin-Chhabra B, Kazory A. A Blueprint for an Integrated Point-of-Care Ultrasound Curriculum for Nephrology Trainees. *Kidney360* 2021; **2**: 1669-1676 [PMID: 35372975 DOI: 10.34067/KID.0005082021]
5 **Turk M**, Robertson T, Koratala A. Point-of-care ultrasound in diagnosis and management of congestive nephropathy. *World J Crit Care Med* 2023; **12**: 53-62 [PMID: 37034023 DOI: 10.5492/wjccm.v12.i2.53]
6 **Bhasin-Chhabra B**, Koratala A. Point of care ultrasonography in onco-nephrology: A stride toward better physical examination. *World J Nephrol* 2023; **12**: 29-39 [PMID: 37035508 DOI: 10.5527/wjn.v12.i2.29]
7 **Johnson JE**, Carpenter JL. Medical house staff performance in physical examination. *Arch Intern Med* 1986; **146**: 937-941 [PMID: 3963985 DOI: 10.1001/archinte.1986.00360170163023]
8 **St Clair EW**, Oddone EZ, Waugh RA, Corey GR, Feussner JR. Assessing housestaff diagnostic skills using a cardiology patient simulator. *Ann Intern Med* 1992; **117**: 751-756 [PMID: 1416578 DOI: 10.7326/0003-4819-117-9-751]
9 **Miglioranza MH**, Gargani L, Sant'Anna RT, Rover MM, Martins VM, Mantovani A, Weber C, Moraes MA, Feldman CJ, Kalil RA, Sicari R, Picano E, Leiria TL. Lung ultrasound for the evaluation of pulmonary congestion in outpatients: a comparison with clinical assessment, natriuretic peptides, and echocardiography. *JACC Cardiovasc Imaging* 2013; **6**: 1141-1151 [PMID: 24094830 DOI: 10.1016/j.jcmg.2013.08.004]
10 **Breidthardt T**, Moreno-Weidmann Z, Uthoff H, Sabti Z, Aeppli S, Puelacher C, Stallone F, Twerenbold R, Wildi K, Kozhuharov N, Wussler D, Flores D, Shrestha S, Badertscher P, Boeddinghaus J, Nestelberger T, Gimenez MR, Staub D, Aschwanden M, Lohrmann J, Pfister O, Osswald S, Mueller C. How accurate is clinical assessment of neck veins in the estimation of central venous pressure in acute heart failure? Insights from a prospective study. *Eur J Heart Fail* 2018; **20**: 1160-1162 [PMID: 29314487 DOI: 10.1002/ejhf.1111]
11 **Martindale JL**, Wakai A, Collins SP, Levy PD, Diercks D, Hiestand BC, Fermann GJ, deSouza I, Sinert R. Diagnosing Acute Heart Failure in the Emergency Department: A Systematic Review and Meta-analysis. *Acad Emerg Med* 2016; **23**: 223-242 [PMID: 26910112 DOI: 10.1111/acem.12878]
12 **Torino C**, Gargani L, Sicari R, Letachowicz K, Ekart R, Fliser D, Covic A, Siamopoulos K, Stavroulopoulos A, Massy ZA, Fiaccadori E, Caiazza A, Bachelet T, Slotki I, Martinez-Castelao A, Coudert-Krier MJ, Rossignol P, Gueler F, Hannedouche T, Panichi V, Wiecek A, Pontoriero G, Sarafidis P, Klinger M, Hojs R, Seiler-Mussler S, Lizzi F, Siriopol D, Balafa O, Shavit L, Tripepi R, Mallamaci F, Tripepi G, Picano E, London GM, Zoccali C. The Agreement between Auscultation and Lung Ultrasound in Hemodialysis Patients: The LUST Study. *Clin J Am Soc Nephrol* 2016; **11**: 2005-2011 [PMID: 27660305 DOI: 10.2215/CJN.03890416]
13 **Lichtenstein D**, Goldstein I, Mourgeon E, Cluzel P, Grenier P, Rouby JJ. Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. *Anesthesiology* 2004; **100**: 9-15 [PMID: 14695718 DOI: 10.1097/00000542-200401000-00006]
14 **Cox EGM**, Koster G, Baron A, Kaufmann T, Eck RJ, Veenstra TC, Hiemstra B, Wong A, Kwee TC, Tulleken JE, Keus F, Wiersema R, van der Horst ICC; SICS Study Group. Should the ultrasound probe replace your stethoscope? A SICS-I sub-study comparing lung ultrasound and pulmonary auscultation in the critically ill. *Crit Care* 2020; **24**: 14 [PMID: 31931844 DOI: 10.1186/s13054-019-2719-8]
15 **Panoulas VF**, Daigeler AL, Malaweera AS, Lota AS, Baskaran D, Rahman S, Nihoyannopoulos P. Pocket-size hand-held cardiac ultrasound as an adjunct to clinical examination in the hands of medical students and junior doctors. *Eur Heart J Cardiovasc Imaging* 2013; **14**: 323-330 [PMID: 22833550 DOI: 10.1093/ehjci/jes140]
16 **Mjølstad OC**, Andersen GN, Dalen H, Graven T, Skjetne K, Kleinau JO, Haugen BO. Feasibility and reliability of point-of-care pocket-size echocardiography performed by medical residents. *Eur Heart J Cardiovasc Imaging* 2013; **14**: 1195-1202 [PMID: 23644936 DOI: 10.1093/ehjci/jet062]
17 **Marbach JA**, Almufleh A, Di Santo P, Jung R, Simard T, McInnes M, Salameh JP, McGrath TA, Millington SJ, Diemer G, West FM, Domecq MC, Hibbert B. Comparative Accuracy of Focused Cardiac Ultrasonography and Clinical Examination for Left Ventricular Dysfunction and Valvular Heart Disease: A Systematic Review and Meta-analysis. *Ann Intern Med* 2019; **171**: 264-272 [PMID: 31382273 DOI: 10.7326/M19-1337]
18 **Koratala A**, Bhattacharya D, Kazory A. Point of care renal ultrasonography for the busy nephrologist: A pictorial review. *World J Nephrol* 2019; **8**: 44-58 [PMID: 31363461 DOI: 10.5527/wjcc.v8.i3.44]
19 **Koratala A**, Ronco C, Kazory A. Multi-Organ Point-Of-Care Ultrasound in Acute Kidney Injury. *Blood Purif* 2022; **51**: 967-971 [PMID: 35306497 DOI: 10.1159/000522652]
20 **Romero-González G**, Manrique J, Slon-Roblero MF, Husain-Syed F, De la Espriella R, Ferrari F, Bover J, Ortiz A, Ronco C. PoCUS in nephrology: a new tool to improve our diagnostic skills. *Clin Kidney J* 2023; **16**: 218-229 [PMID: 36755847 DOI: 10.1093/ckj/sfac203]
21 **Koratala A**, Reisinger N. Point of Care Ultrasound in Cirrhosis-Associated Acute Kidney Injury: Beyond Inferior Vena Cava. *Kidney360* 2022; **3**: 1965-1968 [PMID: 36514396 DOI: 10.34067/KID.0005522022]
22 **AMA**. H-230.960 Privileging for Ultrasound Imaging. [cited 10 June 2023]. Available from: https://policysearch.ama-assn.org/policyfinder/detail/Ultrasoundimaging?uri=%2FAMADoc%2FHOD.xml-0-1591.xml
23 **Nephropocus**. How to get certified in POCUS? [cited 10 June 2023]. Available from: https://nephropocus.com/2020/11/05/how-to-get-certified-in-pocus/

24 **Szabó GV**, Szigetváry C, Szabó L, Dembrovszky F, Rottler M, Ocskay K, Madzsar S, Hegyi P, Molnár Z. Point-of-care ultrasound improves clinical outcomes in patients with acute onset dyspnea: a systematic review and meta-analysis. *Intern Emerg Med* 2023; **18**: 639-653 [PMID: 36310302 DOI: 10.1007/s11739-022-03126-2]

25 **Brogi E**, Bignami E, Sidoti A, Shawar M, Gargani L, Vetrugno L, Volpicelli G, Forfori F. Could the use of bedside lung ultrasound reduce the number of chest x-rays in the intensive care unit? *Cardiovasc Ultrasound* 2017; **15**: 23 [PMID: 28903756 DOI: 10.1186/s12947-017-0113-8]

26 **Barchiesi M**, Bulgheroni M, Federici C, Casella F, Medico MD, Torzillo D, Janu VP, Tarricone R, Cogliati C. Impact of point of care ultrasound on the number of diagnostic examinations in elderly patients admitted to an internal medicine ward. *Eur J Intern Med* 2020; **79**: 88-92 [PMID: 32703675 DOI: 10.1016/j.ejim.2020.06.026]

27 **Loutradis C**, Papadopoulos CE, Sachpekidis V, Ekart R, Krunic B, Karpetas A, Bikos A, Tsouchnikas I, Mitsopoulos E, Papagianni A, Zoccali C, Sarafidis P. Lung Ultrasound-Guided Dry Weight Assessment and Echocardiographic Measures in Hypertensive Hemodialysis Patients: A Randomized Controlled Study. *Am J Kidney Dis* 2020; **75**: 11-20 [PMID: 31732234 DOI: 10.1053/j.ajkd.2019.07.025]

28 **Loutradis C**, Sarafidis PA, Ekart R, Papadopoulos C, Sachpekidis V, Alexandrou ME, Papadopoulou D, Efstratiadis G, Papagianni A, London G, Zoccali C. The effect of dry-weight reduction guided by lung ultrasound on ambulatory blood pressure in hemodialysis patients: a randomized controlled trial. *Kidney Int* 2019; **95**: 1505-1513 [PMID: 31027889 DOI: 10.1016/j.kint.2019.02.018]

29 **Andersen CA**, Brodersen J, Rudbæk TR, Jensen MB. Patients' experiences of the use of point-of-care ultrasound in general practice - a cross-sectional study. *BMC Fam Pract* 2021; **22**: 116 [PMID: 34144701 DOI: 10.1186/s12875-021-01459-z]

30 **Mathews BK**, Miller PE, Olson APJ. Point-of-Care Ultrasound Improves Shared Diagnostic Understanding Between Patients and Providers. *South Med J* 2018; **111**: 395-400 [PMID: 29978223 DOI: 10.14423/SMJ.0000000000000833]

31 **Koratala A**. Point of Care Ultrasonography Enhanced Physical Examination: A Nephrologist's Perspective. *Am J Med* 2020; **133**: e384-e385 [PMID: 32600549 DOI: 10.1016/j.amjmed.2020.01.015]

32 **Andersen CA**, Holden S, Vela J, Rathleff MS, Jensen MB. Point-of-Care Ultrasound in General Practice: A Systematic Review. *Ann Fam Med* 2019; **17**: 61-69 [PMID: 30670398 DOI: 10.1370/afm.2330]

33 Ultrasound Guidelines: Emergency, Point-of-Care and Clinical Ultrasound Guidelines in Medicine. *Ann Emerg Med* 2017; **69**: e27-e54 [PMID: 28442101 DOI: 10.1016/j.annemergmed.2016.08.457]

34 **Romero-González G**, Argaiz ER, Koratala A, Ariel Gonzalez D, Vives M, Juega J, Soler-Majoral J, Graterol F, Perezpaya, Rodrigues-Chivita N, o Lorenzo-Ferris I, Narvaez C, Manriqe J, Morales E, Rivera-Gorrín M, Ibeas J, Bover J, Sanchez E, de Sequera P. Hacia la estandarización de la formación de PoCUS en nefrología: el momento es ahora. *Nefrologia* 2023 [DOI: 10.1016/j.nefro.2023.01.003]

35 **Koratala A**, Bhattacharya D, Kazory A. Harnessing Twitter polls for multi-specialty collaboration in standardizing point-of-care ultrasonography in nephrology. *Clin Nephrol* 2020; **94**: 50-52 [PMID: 32324128 DOI: 10.5414/CN109946]

36 **Blaivas M**, Pawl R. Analysis of lawsuits filed against emergency physicians for point-of-care emergency ultrasound examination performance and interpretation over a 20-year period. *Am J Emerg Med* 2012; **30**: 338-341 [PMID: 21277134 DOI: 10.1016/j.ajem.2010.12.016]

37 **Stolz L**, O'Brien KM, Miller ML, Winters-Brown ND, Blaivas M, Adhikari S. A review of lawsuits related to point-of-care emergency ultrasound applications. *West J Emerg Med* 2015; **16**: 1-4 [PMID: 25671000 DOI: 10.5811/westjem.2014.11.23592]

38 **Nguyen J**, Cascione M, Noori S. Analysis of lawsuits related to point-of-care ultrasonography in neonatology and pediatric subspecialties. *J Perinatol* 2016; **36**: 784-786 [PMID: 27078203 DOI: 10.1038/jp.2016.66]

39 **Reaume M**, Farishta M, Costello JA, Gibb T, Melgar TA. Analysis of lawsuits related to diagnostic errors from point-of-care ultrasound in internal medicine, paediatrics, family medicine and critical care in the USA. *Postgrad Med J* 2021; **97**: 55-58 [PMID: 32457206 DOI: 10.1136/postgradmedj-2020-137832]

40 **Russ B**, Arthur J, Lewis Z, Snead G. A review of lawsuits related to point-of-care emergency ultrasound applications. *J Emerg Med* 2022; **63**: 661-672 [PMID: 35953324 DOI: 10.1016/j.jemermed.2022.04.020]

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MINIREVIEWS

Cryptococcosis in kidney transplant recipients: Current understanding and practices

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Abstract

Cryptococcosis is the third most commonly occurring invasive fungal disease in solid organ transplant recipients (SOT). It is caused by encapsulated yeast, Cryptococcus species, predominantly Cryptococcus neoformans and Cryptococcus gattii. Though kidney transplant recipients are at the lowest risk of cryptococcosis when compared to other solid organ transplant recipients such as lung, liver or heart, still this opportunistic infection causes significant morbidity and mortality in this subset of patients. Mortality rates with cryptococcosis range from 10%-25%, while it can be as high as 50% in SOT recipients with central nervous system involvement. The main aim of diagnosis is to find out if there is any involvement of the central nervous system in disseminated disease or whether there is only localized pulmonary involvement as it has implications for both prognostication and treatment. Detection of cryptococcal antigen (CrAg) in cerebrospinal fluid or plasma is a highly recommended test as it is more sensitive and specific than India ink and fungal cultures. The CrAg lateral flow assay is the single point of care test that can rapidly detect cryptococcal polysaccharide capsule. Treatment of cryptococcosis is challenging in kidney transplant recipients. Apart from the reduction or optimization of immunosuppression, lipid formulations of amphotericin B are preferred as induction antifungal agents. Consolidation and maintenance are done with fluconazole; carefully monitoring

its interactions with calcineurin inhibitors. This review further discusses in depth the evolving developments in the epidemiology, pathogenesis, diagnostic assays, and management approach of cryptococcosis in kidney transplant recipients.

Key Words: Cryptococcosis; Kidney transplant recipients; Amphotericin B; Immunosuppression; Fluconazole

Core Tip: Cryptococcosis is the third most common invasive fungal infection in solid organ transplant recipients. As an opportunistic infection, it poses substantial morbidity and mortality in kidney transplant recipients. Mortality rates for cryptococcosis range from 10% to 25%. In immunocompromised patients, especially in cryptococcus-endemic areas, cryptococcosis must be suspected and diagnosed with a low threshold. Compared to India ink and fungal cultures, tests for the cryptococcal antigen detection in cerebrospinal fluid or plasma test are more sensitive and specific. The management of cryptococcosis poses considerable difficulties, mostly done with reduction or optimization of immunosuppression in addition to lipid formulations of amphotericin B and fluconazole.

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INTRODUCTION

With the advent of a successful kidney transplantation way back in 1954, we have been able to ensure good initial graft outcomes with potent immunosuppression. Though potent, these drugs have their own side effect profiles[1]. Amongst these side effects, the most profound is higher rates of infections. Fungal infections occur in 15%-42% of organ transplant recipients. However, newer antifungal drugs have ensured a decline in these rates, especially invasive candidate infection. Cryptococcal infections generally are seen in the late post-transplant period, the time when anti-fungal prophylaxis is stopped[2]. Majority of these infections are due to the reactivation of pre-existing latent infections. Mortality rates are variable ranging from 33%-40% and are highest in those with central nervous system involvement[3]. Calcineurin inhibitors interestingly have anti-fungal activity in vitro. Tacrolimus showed more promising antifungal activity compared to cyclosporin and that might be due to efflux pump inhibition which is not present in cyclosporin[4]. Mammalian target of rapamycin inhibitors like rapamycin, and everolimus exhibit *in vitro* antifungal activity[5,6]. This however may not be truly protective against fungal infection in the real world. Considering the high mortality and even higher morbidity, there is a growing need for easily available highly specific diagnostic modalities for early diagnosis and treatment initiation. In this manuscript, we highlight the disease burden, the latest identification tools and outcomes in renal allograft recipients with present-day immunosuppression and anti-fungal therapy.

MICROBIOLOGY OF CRYPTOCOCCUS

Cryptococcus is a genus of basidiomycetous fungi with more than thirty species commonly found in the environment. There are only two species commonly known to be pathogenic, C neoformans and C gattii. C neoformans was first identified as human pathogen in the late 19th century but was recognized as a common human causative organism of human disease in late 1970s[7]. The pathogenic yeasts can be subclassified into four serotypes based upon capsular agglutination reactions and are designated A, B, C or D. From a clinical prospective it is reasonable to divide cryptococcus into two species complexes: C neoformans (serotype A, D) and c gattii (serotype B, C)[8]. Majority of cryptococcal infection (around 95%) are caused by C neoformans serotype A where as only 4%-5% infections are caused by C neoformans serotype D or C gattii serotype B, C. C neoformans is found throughout the world in association with birds excreta like pigeons, environmental scavengers like amoeba and in a variety of tree species. C gattii is commonly associated with several species of trees in tropical and subtropical climates[9-11]. The life cycle of cryptococcus involves both asexual and sexual forms. The asexual form exists as haploid encapsulated yeast and reproduces by budding. The yeasts are the only form of cryptococcus that have isolated from human infections. The sexual form is observed only in the laboratory[12]. Cryptococcus causes infection following inhalation of aerosolized infectious particles like desiccated yeast cells and basidiospores through the respiratory tract. Cryptococcal infection is acquired from the environment and the spread of infection from person to person has not been documented except with transplanted tissue[7,13].

EPIDEMIOLOGY

Cryptococcosis is an important opportunistic infection that leads to significant morbidity and mortality in transplant recipients. In solid organ transplant (SOT) recipients, it is the third most commonly occurring invasive fungal infection (IFI) after candidiasis and aspergillosis[14]. Though one recent retrospective observational study from Northern India highlighted the recent rise in angio-invasive fungal infections like mucormycosis and aspergillosis. Cryptococcosis was the fourth most commonly reported infection in this study preceded by mucormycosis, aspergillosis and pneumocystis jiroveci[15].

Cryptococcosis accounts for 8-10% of the invasive fungal infections in SOT recipients[15]. Its overall incidence in various cohorts of SOT recipients ranges from 0.2% to 5% depending on the type of organ transplanted[14,16,17]. As per a recently published retrospective analysis of the cohort of patients after organ transplantation from three states of the United States, the incidence of cryptococcosis was 0.32% after kidney transplantation which was lower than both lung and liver transplant recipients[18]. Shenoy *et al*[19] in their recent retrospective analysis showed a very low incidence of 0.04%.

Cryptococcosis primarily occurs due to the reactivation of the latent infection in the post-transplant period[20]. Two decades back, it occurred primarily amongst patients with human immunodeficiency virus (HIV), but now the majority of infections occur in non-HIV population, particularly immunosuppressed SOT recipients (60%-70% of the total cases)[21]. This may be explained by the emergence of highly active antiretroviral therapy for the treatment of HIV, along with an increase in the number of patients undergoing transplantation and the use of immunosuppressants. Calcineurin inhibitors (CNI) can affect the extent of the disease. Patients receiving CNIs were less likely to have disseminated disease due to their *in vitro* antifungal properties by targeting fungal homologs of calcineurin[22]. Steroids and T cell-depleting induction agents (antithymocyte or alemtuzumab) are associated with an increased risk of cryptococcosis[23,24].

Cryptococcosis is a late-occurring invasive fungal infection (after 1 year). It has a longer (574 d) median time to onset from the date of transplant as compared to invasive candidiasis (103 d) and aspergillosis (184 d)[25]. Based on the organ transplanted, the median time to onset is earlier after lung (191 d), heart (195 d) and liver (200 d) as compared to kidney transplantation (616 d)[18].

Mortality rates with cryptococcosis range from 10%-25%, while it can be as high as 50 % in SOT recipients with cryptococcal meningitis[26].

PATHOPHYSIOLOGY

C. neoformans is detected by a number of innate receptors, including Toll-like receptors, mannose receptors and -glucan receptors in the body during infection. Cells of innate immunity such as natural killer cells, dendritic cells, macrophages and neutrophils are primarily involved in C. neoformans killing in the host[27]. In particular, the establishment of Th1 and Th17 responses following the activation of macrophages is responsible for fungus clearance. Th1 and Th17 cells produce inflammatory cytokines such as IFN-, IL-17, and IL-22 in response to C. neoformans infection, resulting in robust antimicrobial and phagocytic responses[28]. Recently, studies have shown that mediators of death receptor-triggered extrinsic apoptosis, FADD and RIPK3 (immune regulators) control excessive inflammation during C. neoformans infection[29]. Replication of C. neoformans inside macrophages has been shown to be directly correlated with the susceptibility of the host to infection. Factors and conditions that modulate macrophage function causing T-cell function impairment such as in recipients of SOT can result in cryptococcal disease as a result of the reduced antifungal capacity of cells, facilitating the intracellular growth of C. neoformans[30]. C. neoformans releases an array of molecules such as prostaglandins and leukotrienes and virulence-associated enzymes that alter the local immune response of the host by having direct effects on inflammatory cells. Cryptococcal polysaccharides interfere with the migration of leukocytes toward chemoattractants[31]. The robust immune responses can at times be destructive to the organs of the host, especially to the lung parenchyma. Mouse models suggest CD4+ T cells mediates inflammation and host damage in the setting of C. neoformans infection[32]. Rarely, transmission can also occur from a donor allograft[33].

CLINICAL MANIFESTATION

Depending on the host's immunological condition, clinical signs of cryptococcal infection in a kidney transplant recipients (KTR) might range from asymptomatic colonization of the respiratory tract to wide dissemination[34]. The central nervous system (CNS) is the primary target site. C. neoformans is typically acquired through inhalation into the lungs, where it can spread to the skin, bone, myocardium, transplanted kidney and other organs. The cryptococcal infection in kidney transplant recipients might be the result of a recent acquisition or the recurrence of a latent or dormant infection. Epidemiological data has long suggested that cryptococcal infections exhibit dormancy and reactivation[22]. Cryptococcus neoformans possess the traits required for dormant infection in humans. In an analysis, of 52% of transplant recipients with cryptococcosis, there was evidence of a latent infection before the organ transplant[35]. Figure 1 shows various organ involvement of the human body in cryptococcal infection.

Up to 70% of patients with cryptococcal illness have involvement of the central nervous system. Leptomeningeal or parenchymal lesions, as well as hydrocephalus, can be seen. Frequent clinical signs of CNS involvement include fever, headache, altered mental status, vomiting, seizure, and visual and auditory complaints[36].

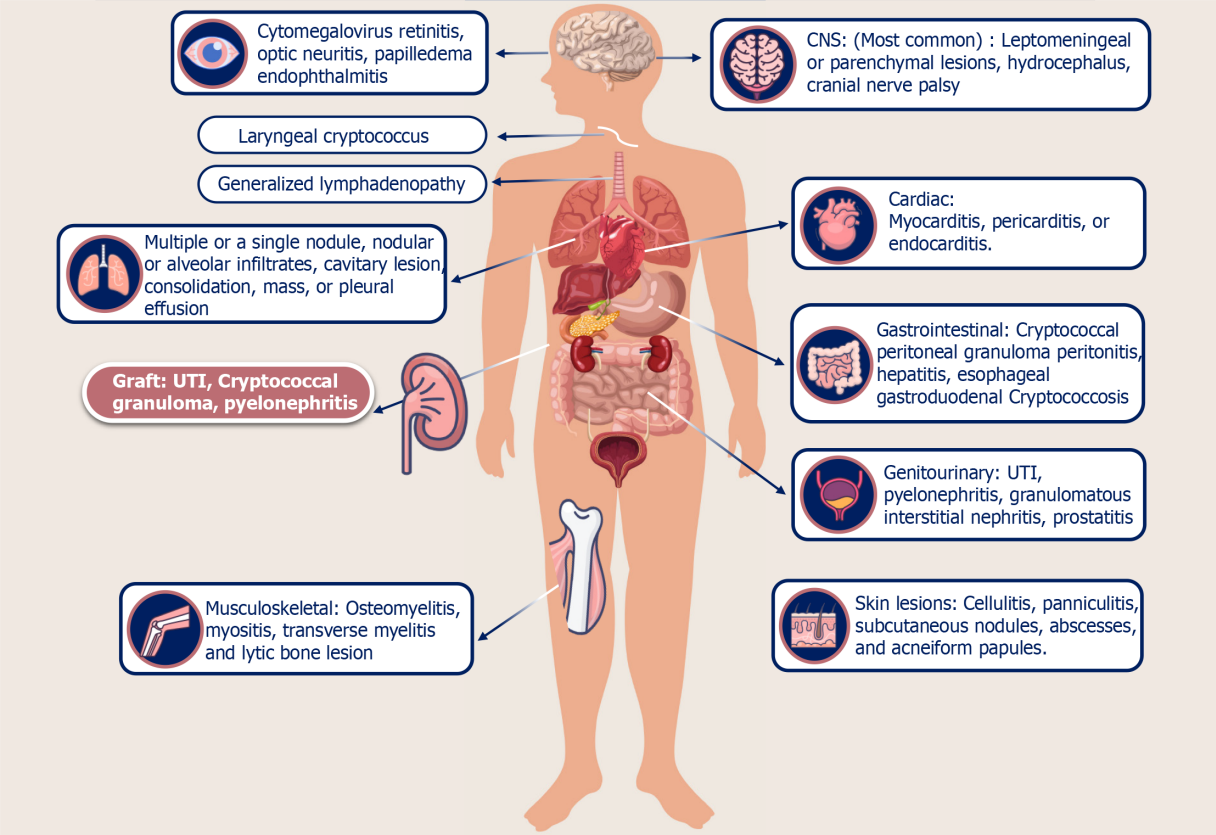

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Figure 1 Various organ involvement of the human body in cryptococcal infection. UTI: Urinary tract infection; CNS: Central nervous system.

Other major organs affected include the lungs, skin, soft tissues, and osteoarticular. Generalized lymphadenopathy with constitutional symptoms and weight loss can be a presentation that can mimic post transplant lymphoproliferative disease.

The typical signs of pulmonary involvement in a cryptococcus infection include fever, lethargy, night sweats, weight loss, sputum-producing cough, dyspnea, hemoptysis, and rarely severe respiratory failure. Only about one-third of people with cryptococcosis have a lung-only disease, which is usually part of an infection that has spread to other parts of the body[30]. A chest X-ray may reveal multiple or a single nodule, nodular or alveolar infiltrates, a cavitary lesion, a consolidation, a mass, or a pleural effusion. One-third or more of patients with pulmonary cryptococcosis may be asymptomatic[37]. Compared to patients with consolidations, pleural effusions, and infiltrates, patients with nodular densities or mass lesions were less likely to be symptomatic. Rarely severe cryptococcal infection especially with lung involvement can be complicated by the development of hemophagocytic lymphohistiocytosis (HLH) associated with very high mortality. A high index of suspicion is needed to make an early diagnosis which can help to incorporate specific therapy for HLH earlier which may improve outcomes[38].

Rarely, skin involvement is also seen with cryptococcal infection. Studies have shown that skin involvement can be the first sign of a disseminated cryptococcal illness[39]. Primary cutaneous cryptococcosis may act as a portal of entry for secondary disseminated cryptococcosis. Skin lesions might include cellulitis, panniculitis, subcutaneous nodules, abscesses, and acneiform papules. Umbilicated papules resembling Molluscum contagiosum are often present in hemogenous cryptococcal skin changes.

Another condition for the disease's localized form is cryptococcoma[33]. Most of them are recognized radiologically. Localized cryptococcal lesions typically coexist with a systemic illness. These are more typical in infections caused by Cryptococcus gattii. Cryptococcoma mainly affects the CNS and very infrequently the lungs and the transplanted kidney.

Both symptomatic cryptococcal pyelonephritis and graft involvement have been reported in cryptococcal infection[40]. Laryngeal cryptococcus and renal arterial rupture related to cryptococcus have also been described[41,42].

DIAGNOSIS OF CRYPTOCOCCAL INFECTION

Diagnosis can be challenging, especially in transplant recipients. One must have a high index of suspicion and a low diagnostic threshold to diagnose cryptococcosis, especially in regions with high prevalence. Any clinical signs of disease like subacute headache, fever, cough and weakness should prompt rapid cryptococcal testing. All transplant recipients with suspected or proven cryptococcosis should undergo a thorough evaluation for extrapulmonary sites of infection including a lumbar puncture [large volume cerebrospinal fluid (CSF) sample] and blood/urine cultures. This is important

to delineate the site and extent of disease in order to decide the duration of antifungal treatment. The methods used to confirm the infection include direct microscopic examination, culture, histopathology, serology and molecular detection. Antigen tests from blood or culture are rarely positive unless there is disseminated cryptococcal infection.

Imaging: CNS and chest

Cerebral cryptococcosis are more common with C gatti than with C neoformans infection. Normal brain imaging always does not exclude meningoencephalitis. Magnetic resonance imaging (MRI) (magnetic resonance imaging) brain is the preferred modality of imaging to diagnose cerebral cryptococcosis. The MRI findings of CNS cryptococcosis are leptomeningeal/pachymeningeal enhancement, dilated perivascular space, cryptococcal granuloma, hydrocephalus, miliary nodule and plexitis which can occur in isolation or in various combinations[43]. Chest imaging in pulmonary infection is non-specific with solitary/ multiple nodules or diffuse interstitial infiltrates[37].

CSF examination: The CSF picture in cryptococcal meningoencephalitis classically demonstrates increased opening CSF pressure, low white cell count with a mononuclear predominance, and slightly elevated protein with low/normal glucose concentration[44]. Neuroimaging should be done prior to lumbar puncture to exclude hydrocephalus and mass lesions. Cryptococcal antigen testing from the CSF or serum is the preferred strategy to diagnose infection. India ink testing on CSF is no longer recommended because it can miss low burden infections due to the low sensitivity and specificity.

Microscopy and culture

Visualization of encapsulated yeast forms with narrow budding in the sputum, bronchoalveolar lavage (BAL) or lung tissue biopsy specimens is suggestive of cryptococcal infection. The pellet from pleural fluid or BAL can be mixed with India Ink and observed under a microscope[45]. A lung biopsy from a nodule of uncertain aetiology requires a fungal culture to be done, in addition to a histopathology examination. Samples for culture should be placed on Sabouraud dextrose agar at 30°C for 7 d, in aerobic conditions, and observed daily[46]. Cryptococcus appears as mucoid creamy colonies. C. neoformans are identified generally as smooth colonies while C. gattii mostly appears as mucoid colonies. Canavanine-glycine-bromothymol blue (CGB) agar can be used to differentiate between C. neoformans and C. gattii. Colonies of C. neoformans will not cause changes in CGB agar. On the other hand, C. gattii produces a blue colour in CGB agar.

Histopathology

A lung biopsy is the best diagnostic option when sputum or bronchoscopy specimens are unavailable or negative. Gamori's methenamine silver or periodic acid Schiff stain identifies the organism as narrow-based budding yeasts (4-10 μm), usually surrounded by thick capsules in the lung tissue. Mucicarmine stain can be used to highlight the cryptococcal capsule as rose burgundy. Histopathological methods and cryptococcal antigen testing cannot differentiate between C neoformans and C gattii[47]. Lung histopathology in pulmonary cryptococcal infection varies from well-formed granulomas to minimal inflammation. Positive histology does not always correlate with culture result. A negative culture might be caused by nonviable organisms in the sample[30]. Figure 2 shows the histopathology of a patient with pulmonary cryptococcosis (H & E stain) and Figure 3 shows the histopathology of a patient with pulmonary cryptococcosis (Alcian blue -PAS stain). India Ink of Cryptococcus neoformans is provided in Figure 4.

Cryptococcal antigen testing

Capsular polysaccharides of Cryptococcus can be detected by using specific anti C. neoformans antisera in the serum, CSF, BAL, and urine by two formats- the latex agglutination test and the recently approved lateral flow immunoassay (LFA)[48]. LFA is the preferred method recommended for diagnosis given its low cost and high sensitivity. These cryptococcal antigen (CrAg) detection tests are rapid, sensitive and specific for diagnosis. These tests have not been standardised for respiratory specimens such as BAL, pleural fluid, or sputum. Pulmonary cryptococcal infection is usually associated with false negative serum CrAg, probably because of the low fungal burden outside the lung or the capsule-deficient strain of Cryptococcus[37]. Serum CrAg titres are typically higher in patients with disseminated diseases/CNS involvement. A prozone effect can occur in high cryptococcal burden states and recognition of this with appropriate dilution of the sample may be required.

Molecular detection

This may be required in specific situations where other diagnostic tests have failed to confirm the diagnosis. These molecular methods include pan-fungal polymerase chain reaction (PCR), deoxyribonucleic acid sequencing for identification, multiplex PCR, isothermal amplification method, and probe-based microarrays. Species identification of cryptococcus is also important as it may affect the choice of antifungal therapy and affect the clinical outcomes. Where possible, isolates should be subjected to either PCR or matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) for genotypic identification. Antifungal susceptibility testing is routinely not recommended for cryptococcal infection[49]. However, in patients with C neoformans infection who have failed primary therapy or relapsed, or in patients with recent antifungal exposure (*i.e.* antifungal prophylaxis), antifungal susceptibility testing for fluconazole is recommended[50]. Table 1 shows modalities for the diagnosis of post-transplant cryptococcosis.

Table 1 Modalities for the diagnosis of post-transplant cryptococcosis

Method	Advantages	Disadvantages
Direct microscopic examination	Cryptococcus is identified as narrow budding encapsulated yeasts after mixing sample with India ink.	Direct microscopic examination
Culture	Identify the species and susceptibility patterns	Time consuming. More than 1 wk must elapse for fungal growth to occur
Histopathology	Gomori methenamine silver, and periodic acid-Schiff are used to detect Cryptococcus that appears as narrow-based budding yeasts (4-10 μm), usually surrounded by thick capsules in the lung tissue	Histopathology
Antigen detection	Inexpensive point-of-care testing, simple, cheap and rapid diagnosis in developing country, high sensitivity and specificity	Isolated pulmonary cryptococcal infection is usually associated with false negative serum CrAg, probably because of the low fungal burden outside the lung or the capsule-deficient strain of Cryptococcus. One must be aware of the prozone effectwhile interpreting these tests
Molecular detection	Required in specific situations where other diagnostic tools have failed to confirm a diagnosis of crypto-coccosis, highly specific (almost 100%)	Expensive and not routinely available

CrAg: Cryptococcal antigen.

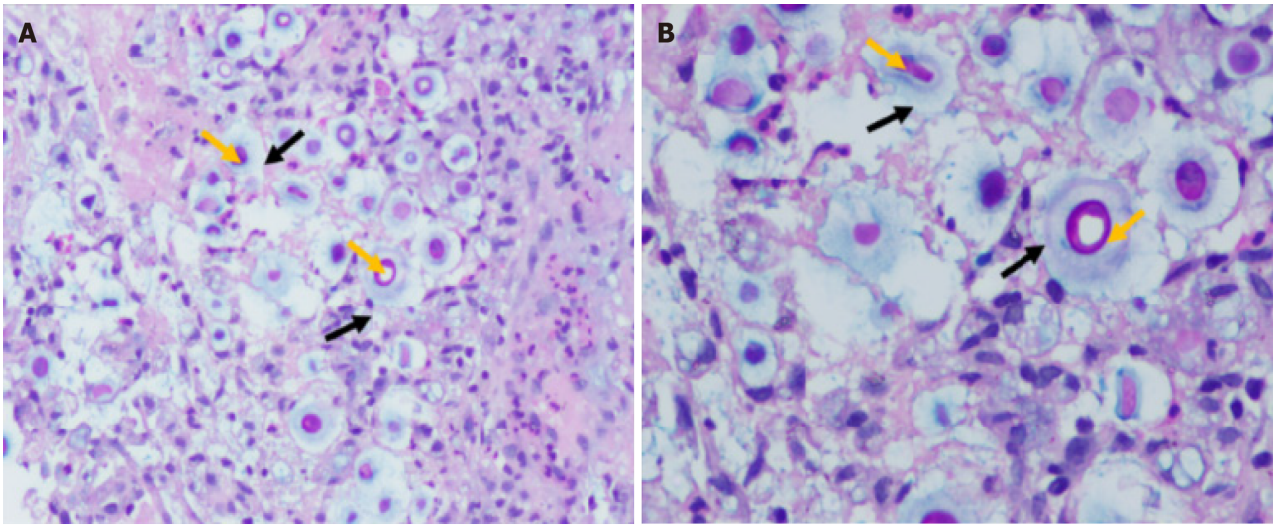

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Figure 2 Histopathology of a patient with pulmonary cryptococcosis, hematoxylin and eosin stain and Alcian blue stain. A: At ×100 magnification; B: At ×200 magnification. Alcian blue-PAS stain atains the yeast forms of cryptococcus. Alcian blue stains the capsule blue colour (black arrow) and PAS stains the cell wall of the yeast magenta colour (yellow arrow).

TREATMENT

Much of the data on the treatment of patients with cryptococcal infections has been extrapolated from trials on HIV Infected patients[51] and also retrospective data from kidney and other SOT patients as there are no randomized controlled trials for the therapy[52-54]. Recommendations herein are consistent with the guidelines of the American Society of Transplantation Infectious Diseases[50].

Management of cryptococcus has 3 main aspects

Antifungal therapy: As discussed, earlier patients with Cryptococcal infections can present with either isolated pulmonary involvement, neurological Involvement or disseminated disease. The Therapy thus also depends on the site and extent of involvement: (1) In patients with CNS disease, Disseminated Disease or Moderate to severe pulmonary involvement the antifungal therapy of choice in kidney transplant recipients would be Liposomal Amphotericin B Conventional amphotericin B is nephrotoxic and found to be inferior to the liposomal form on comparison of 90-d mortality between the two forms[54,55]. The addition of 5-flucytosine as a part of induction therapy reduces the chances of treatment failure[56]. The induction therapy is usually followed by a consolidation phase and maintenance phase. Doses of flucytosine and Fluconazole should be adjusted according to the glomerular filtration rate. Monitoring of flucytosine level is recommended (2 h post-dose 30-80 mcg/mL). Extended doses may be required as per clinical status. Figure 5 shows therapy for patients with CNS disease, Disseminated Disease or Moderate to severe Pulmonary

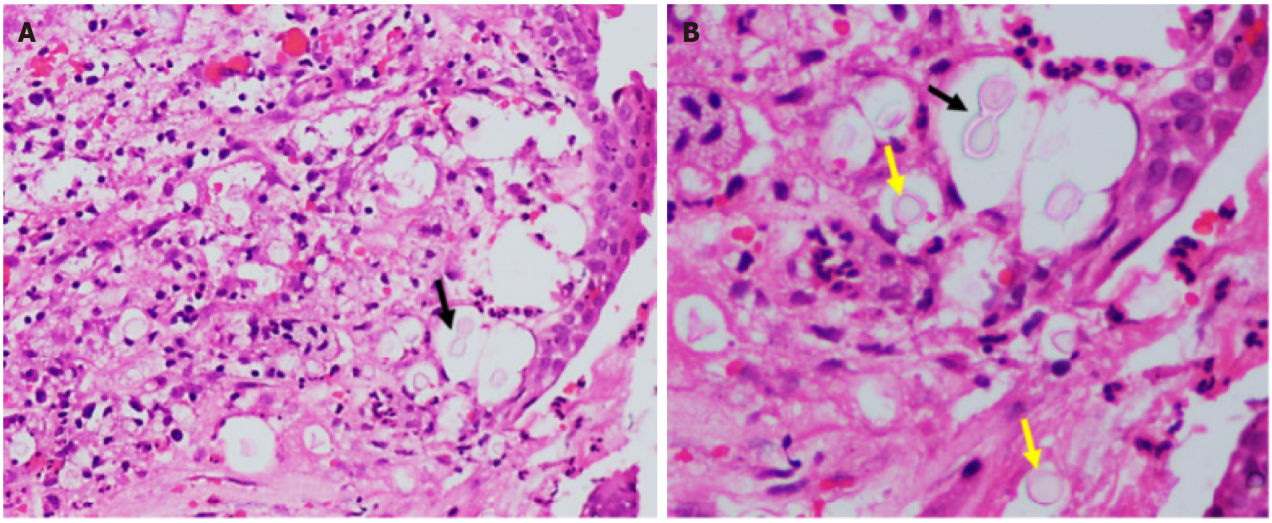

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Figure 3 India ink of cryptococcus neoformans. Endobronchial mucosa shows squamous metaplasia and the sub epithelium shows inflammatory exudates along with variably sized round to oval encapsulated yeast (yellow arrow) with thin walls and narrow based budding (black arrow). A: At ×100 magnification; B: At ×200 magnification.

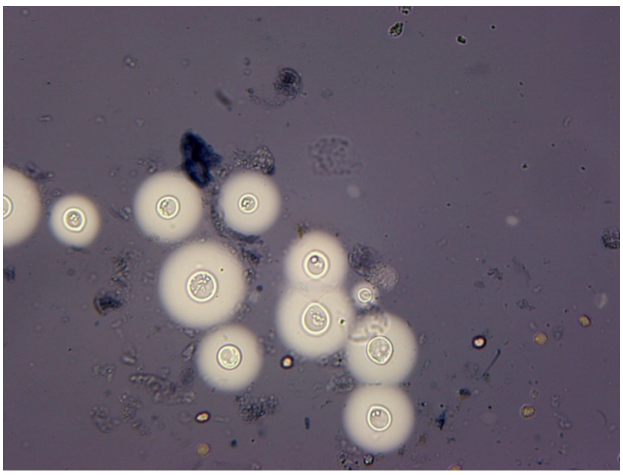

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Figure 4 India ink-stained cryptococcus neoformans.

involvement; and (2) In patients with mild pulmonary disease use of fluconazole 400 mg/d for 6-12 mo is recommended. Even asymptomatically detected (Cryptococcus positive on Sputum culture) pulmonary disease needs to be treated with the same regimen. In all these cases extrapulmonary disease should be excluded. Longer duration of Induction should be considered for patients who are clinically deteriorating, persistent comatose state, and persistently elevated intracranial pressure[16]. In case flucytosine is not available an extended duration of amphotericin B can be used lasting 4-6 wk. Use of extended-spectrum azoles like itraconazole, Voriconazole, Posaconazole, Isavuconazole, do not offer any advantage over fluconazole, but should be used in fluconazole-resistant C. gatti[57,58].

Supportive therapy: (1) Management of elevated Intracranial Pressure: 50% to 70% of patients with cryptococcal meningitis have elevated intracranial pressure due to reduced CSF absorption secondary to a film formed over the pial layer due to significant inflammatory response. This is a significant factor in morbidity and mortality of the patient as it can lead to hydrocephalous, blindness deafness or death[59]. Lumbar puncture should be done in all patients and opening pressure should be noted. If pressure is above 25 mmHg then a large volume of CSF should be removed, and attempts should be made to keep it below 20 mmHg using repeated lumbar puncture or by using drains from CSF cavities to the peritoneum[60]. Maintaining pressures below 25mmhg was associated with 69% relative survival protection[61]; and (2) Use of Dexamethasone: When Dexamethasone was added to adjunctive therapy on HIV patients showed slower clearance of CSF, Increased serious infections and no impact on mortality compared to placebo. But can be used after clearance of infection[62,63].

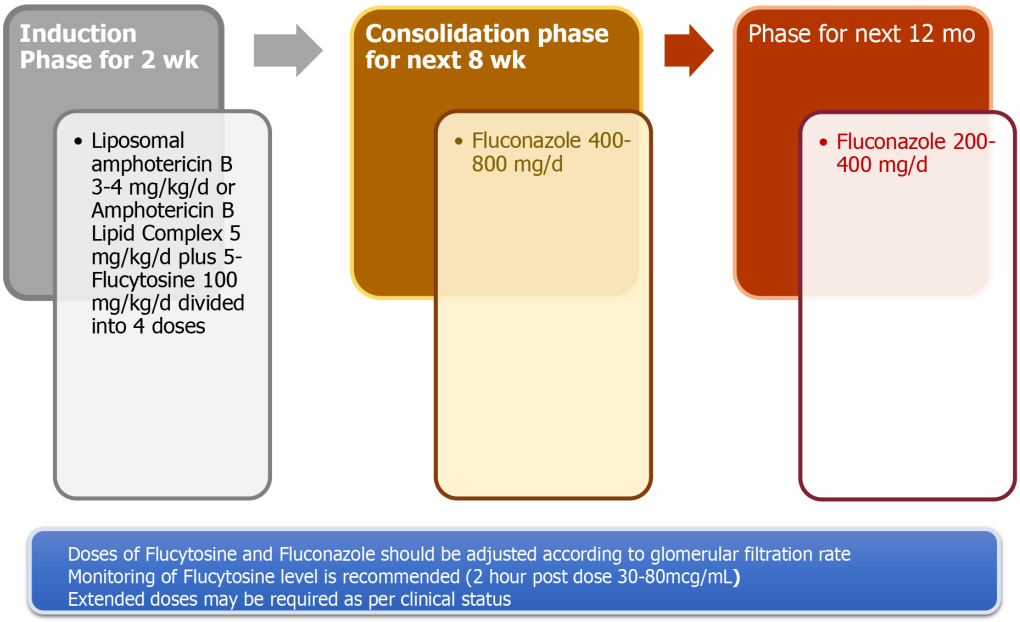

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Figure 5 Therapy for patients with central nervous system disease, disseminated disease or moderate to severe pulmonary involvement.

Change in immunosuppression: As this disease is a direct result of the immunocompromised state of the patient there should be an attempt to reduce the immunosuppressive medications. Although nothing can be done about the T cell depleting agents given in the beginning slow reduction in dose of other immunosuppression with a low threshold for diagnosis of rejection should be done aiming for eradication of the fungus and preservation of allograft. The overall immunosuppression should be minimized during therapy; however, the specific approach to achieve this must be tailored to each individual instance. The expeditious decrease in the administration of immunosuppressive drugs may give rise to unfavorable consequences, including the occurrence of organ rejection and/or immune reconstitution inflammatory syndrome (IRIS). Therefore, it is advisable to strategically implement a progressive decrease in dosage with the administration of antifungal therapy. The primary objective is to achieve complete elimination of the infection while simultaneously ensuring the maintenance of allograft functionality. The interaction of azoles with CNI should be kept in mind and frequent monitoring of levels along with dose reduction should be done. The reduction of immunosuppression in KTR along with antifungal therapy initiation can also lead to the development of IRIS[64]. The incidence of this is 5%-12% in SOT recipients and it mimics a worsening cryptococcal disease and can also lead to rejection and graft loss[21,24,65]. It occurs 4-6 wk after initiation of the therapy and is found to be associated more with CNS disease and stoppage of CNI[16,66]. After ruling out the presence of fungi in the body IRIS can be tackled by increasing the dose of corticosteroids [64,67].

Prognosis and outcomes

Mortality rates in organ transplant recipients with cryptococcosis range from 33%-42% and may be as high as 49% in those with CNS disease and as low as 2.8% in those with isolated pulmonary involvement[2,21,50,51]. Recently, Ponzio *et al*[65] demonstrated an overall mortality rate of 49%. Independent risk factors for mortality include abnormal mental status, renal failure at baseline, fungemia and disseminated infection[24]. Patients receiving tacrolimus are less likely to have central nervous system involvement and more likely to have skin, soft-tissue, and osteoarticular involvement. Improved outcomes with the use of calcineurin-inhibitor agents may be attributable in part to their synergistic interactions with antifungal agents[5,68]. A significant percentage of patients (up to 20%) progress to graft loss after the infection[55]. Risk factors for graft loss after cryptococcosis include disseminated infection, higher baseline creatinine levels, graft dysfunction concomitant with amphotericin B deoxycholate therapy and an additional nephrotoxic condition [56]. Therefore, the clinical focus should be on the use of less nephrotoxic lipid formulations of amphotericin B in this specific population.

CONCLUSION

Cryptococcal infection accounts for < 10% of IFI and is seen in the late transplant period. Mortality rates are higher for those with meningeal involvement. The advent of newer diagnostic modalities and treatment has reduced infection-related morbidity but has not yet been able to reduce mortality beyond a level. Newer therapeutics with liposomal Amphotericin B. Fluconazole, and 5-flucytosine have improved survival. However, a significant proportion of these

patients progress to graft loss either due to reduced immunosuppression, infection or nephrotoxic therapeutic agents. Early detection however has resulted in better survival in the subset of patients.

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FOOTNOTES

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REFERENCES

1 **Kanj SS**, Welty-Wolf K, Madden J, Tapson V, Baz MA, Davis RD, Perfect JR. Fungal infections in lung and heart-lung transplant recipients. Report of 9 cases and review of the literature. *Medicine (Baltimore)* 1996; **75**: 142-156 [PMID: 8965683 DOI: 10.1097/00005792-199605000-00004]

2 **Fortún J**, Martín-Davila P, Moreno S, Barcena R, de Vicente E, Honrubia A, García M, Nuño J, Candela A, Uriarte M, Pintado V. Prevention of invasive fungal infections in liver transplant recipients: the role of prophylaxis with lipid formulations of amphotericin B in high-risk patients. *J Antimicrob Chemother* 2003; **52**: 813-819 [PMID: 14563893 DOI: 10.1093/jac/dkg450]

3 **John GT**, Mathew M, Snehalatha E, Anandi V, Date A, Jacob CK, Shastry JC. Cryptococcosis in renal allograft recipients. *Transplantation* 1994; **58**: 855-856 [PMID: 7940723 DOI: 10.1097/00007890-199410150-00020]

4 **Borba-Santos LP**, Reis de Sá LF, Ramos JA, Rodrigues AM, de Camargo ZP, Rozental S, Ferreira-Pereira A. Tacrolimus Increases the Effectiveness of Itraconazole and Fluconazole against Sporothrix spp. *Front Microbiol* 2017; **8**: 1759 [PMID: 28966608 DOI: 10.3389/fmicb.2017.01759]

5 **Jiang H**, Xiong J, Tan L, Jin P, Sun Y, Yang L, Tan J. In Vitro Interactions of Antifungal Agents and Everolimus Against Aspergillus Species. *Front Cell Infect Microbiol* 2022; **12**: 936814 [PMID: 35865820 DOI: 10.3389/fcimb.2022.936814]

6 **Rohde JR**, Cardenas ME. Nutrient signaling through TOR kinases controls gene expression and cellular differentiation in fungi. *Curr Top Microbiol Immunol* 2004; **279**: 53-72 [PMID: 14560951 DOI: 10.1007/978-3-642-18930-2_4]

7 **Kwon-Chung KJ**, Bennett JE, Wickes BL, Meyer W, Cuomo CA, Wollenburg KR, Bicanic TA, Castañeda E, Chang YC, Chen J, Cogliati M, Dromer F, Ellis D, Filler SG, Fisher MC, Harrison TS, Holland SM, Kohno S, Kronstad JW, Lazera M, Levitz SM, Lionakis MS, May RC, Ngamskulrongroj P, Pappas PG, Perfect JR, Rickerts V, Sorrell TC, Walsh TJ, Williamson PR, Xu J, Zelazny AM, Casadevall A. The Case for Adopting the "Species Complex" Nomenclature for the Etiologic Agents of Cryptococcosis. *mSphere* 2017; **2** [PMID: 28101535 DOI: 10.1128/mSphere.00357-16]

8 **MacDougall L**, Fyfe M, Romney M, Starr M, Galanis E. Risk factors for Cryptococcus gattii infection, British Columbia, Canada. *Emerg Infect Dis* 2011; **17**: 193-199 [PMID: 21291588 DOI: 10.3201/eid1702.101020]

9 **Steenbergen JN**, Shuman HA, Casadevall A. Cryptococcus neoformans interactions with amoebae suggest an explanation for its virulence and intracellular pathogenic strategy in macrophages. *Proc Natl Acad Sci U S A* 2001; **98**: 15245-15250 [PMID: 11742090 DOI: 10.1073/pnas.261418798]

10 **Ellis DH**, Pfeiffer TJ. Natural habitat of Cryptococcus neoformans var. gattii. *J Clin Microbiol* 1990; **28**: 1642-1644 [PMID: 2199524 DOI: 10.1128/jcm.28.7.1642-1644.1990]

11 **EMMONS CW**. Saprophytic sources of Cryptococcus neoformans associated with the pigeon (Columba livia). *Am J Hyg* 1955; **62**: 227-232 [PMID: 13268414 DOI: 10.1093/oxfordjournals.aje.a119775]

12 **Hull CM**, Heitman J. Genetics of Cryptococcus neoformans. *Annu Rev Genet* 2002; **36**: 557-615 [PMID: 12429703 DOI: 10.1146/annurev.genet.36.052402.152652]

13 **Saul N**, Krockenberger M, Carter D. Evidence of recombination in mixed-mating-type and alpha-only populations of Cryptococcus gattii sourced from single eucalyptus tree hollows. *Eukaryot Cell* 2008; **7**: 727-734 [PMID: 18281600 DOI: 10.1128/EC.00020-08]

14 **Pappas PG**, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, Anaissie EJ, Brumble LM, Herwaldt L, Ito J, Kontoyiannis DP, Lyon GM, Marr KA, Morrison VA, Park BJ, Patterson TF, Perl TM, Oster RA, Schuster MG, Walker R, Walsh TJ, Wannemuehler KA, Chiller TM. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Clin Infect Dis* 2010; **50**: 1101-1111 [PMID: 20218876 DOI: 10.1086/651262]

15 **Gupta KL**, Bagai S, Ramachandran R, Kumar V, Rathi M, Kohli HS, Sharma A, Chakrabarti A. Fungal infection in post-renal transplant patient: Single-center experience. *Indian J Pathol Microbiol* 2020; **63**: 587-592 [PMID: 33154310 DOI: 10.4103/IJPM.IJPM_306_19]

16 **Perfect JR**, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, Harrison TS, Larsen RA, Lortholary O, Nguyen MH, Pappas PG, Powderly WG, Singh N, Sobel JD, Sorrell TC. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. *Clin Infect Dis* 2010; **50**: 291-322 [PMID: 20047480 DOI: 10.1086/649858]

17 **Shoham S**, Marr KA. Invasive fungal infections in solid organ transplant recipients. *Future Microbiol* 2012; **7**: 639-655 [PMID: 22568718 DOI: 10.2217/fmb.12.28]

18 **George IA**, Santos CAQ, Olsen MA, Powderly WG. Epidemiology of Cryptococcosis and Cryptococcal Meningitis in a Large Retrospective Cohort of Patients After Solid Organ Transplantation. *Open Forum Infect Dis* 2017; **4**: ofx004 [DOI: 10.1093/ofid/ofv131.53]

19 **Shenoy R**, Prasad N, Kaul A, Bhadauria DS. POS-106 Profile of cryptococcal infections in renal transplant recipients in a tertiary care hospital in North India. *Kidney Int Rep* 2022; **7**: S514-S515 [DOI: 10.1016/j.ekir.2022.07.124]

20 **Garcia-Hermoso D**, Janbon G, Dromer F. Epidemiological evidence for dormant Cryptococcus neoformans infection. *J Clin Microbiol* 1999; **37**: 3204-3209 [PMID: 10488178 DOI: 10.1128/JCM.37.10.3204-3209.1999]

21 **Patel V**, Desjardins M, Cowan J. Shift in Epidemiology of Cryptococcal Infections in Ottawa with High Mortality in Non-HIV Immunocompromised Patients. *J Fungi (Basel)* 2019; **5** [PMID: 31717662 DOI: 10.3390/jof5040104]

22 **Singh N**, Alexander BD, Lortholary O, Dromer F, Gupta KL, John GT, del Busto R, Klintmalm GB, Somani J, Lyon GM, Pursell K, Stosor V, Munoz P, Limaye AP, Kalil AC, Pruett TL, Garcia-Diaz J, Humar A, Houston S, House AA, Wray D, Orloff S, Dowdy LA, Fisher RA, Heitman J, Wagener MM, Husain S; Cryptococcal Collaborative Transplant Study Group. Cryptococcus neoformans in organ transplant recipients: impact of calcineurin-inhibitor agents on mortality. *J Infect Dis* 2007; **195**: 756-764 [PMID: 17262720 DOI: 10.1086/511438]

23 **Silveira FP**, Husain S, Kwak EJ, Linden PK, Marcos A, Shapiro R, Fontes P, Marsh JW, de Vera M, Tom K, Thai N, Tan HP, Basu A, Soltys K, Paterson DL. Cryptococcosis in liver and kidney transplant recipients receiving anti-thymocyte globulin or alemtuzumab. *Transpl Infect Dis* 2007; **9**: 22-27 [PMID: 17313467 DOI: 10.1111/j.1399-3062.2006.00149.x]

24 **Diamond RD**, Bennett JE. Prognostic factors in cryptococcal meningitis. A study in 111 cases. *Ann Intern Med* 1974; **80**: 176-181 [PMID: 4811791 DOI: 10.7326/0003-4819-80-2-176]

25 **Maziarz EK**, Perfect JR. Cryptococcosis. *Infect Dis Clin North Am* 2016; **30**: 179-206 [PMID: 26897067 DOI: 10.1016/j.idc.2015.10.006]

26 **Neofytos D**, Fishman JA, Horn D, Anaissie E, Chang CH, Olyaei A, Pfaller M, Steinbach WJ, Webster KM, Marr KA. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. *Transpl Infect Dis* 2010; **12**: 220-229 [PMID: 20113459 DOI: 10.1111/j.1399-3062.2010.00492.x]

27 **Casadevall A**, Coelho C, Alanio A. Mechanisms of Cryptococcus neoformans-Mediated Host Damage. *Front Immunol* 2018; **9**: 855 [PMID: 29760698 DOI: 10.3389/fimmu.2018.00855]

28 **Alanio A**, Desnos-Ollivier M, Dromer F. Dynamics of Cryptococcus neoformans-macrophage interactions reveal that fungal background influences outcome during cryptococcal meningoencephalitis in humans. *mBio* 2011; **2** [PMID: 21828220 DOI: 10.1128/mBio.00158-11]

29 **Fa Z**, Xie Q, Fang W, Zhang H, Xu J, Pan W, Olszewski MA, Deng X, Liao W. RIPK3/Fas-Associated Death Domain Axis Regulates Pulmonary Immunopathology to Cryptococcal Infection Independent of Necroptosis. *Front Immunol* 2017; **8**: 1055 [PMID: 28919893 DOI: 10.3389/fimmu.2017.01055]

30 **Setianingrum F**, Rautemaa-Richardson R, Denning DW. Pulmonary cryptococcosis: A review of pathobiology and clinical aspects. *Med Mycol* 2019; **57**: 133-150 [PMID: 30329097 DOI: 10.1093/mmy/myy086]

31 **Yauch LE**, Lam JS, Levitz SM. Direct inhibition of T-cell responses by the Cryptococcus capsular polysaccharide glucuronoxylomannan. *PLoS Pathog* 2006; **2**: e120 [PMID: 17096589 DOI: 10.1371/journal.ppat.0020120]

32 **Zaragoza O**, Alvarez M, Telzak A, Rivera J, Casadevall A. The relative susceptibility of mouse strains to pulmonary Cryptococcus neoformans infection is associated with pleiotropic differences in the immune response. *Infect Immun* 2007; **75**: 2729-2739 [PMID: 17371865 DOI: 10.1128/IAI.00094-07]

33 **Santos DWCL**, Hagen F, Meis JF, Cristelli MP, Viana LA, Bernardi FDC, Tedesco-Silva H, Medina-Pestana JO, Colombo AL. Donor-Derived Transmission of Cryptococcus gattii sensu lato in Kidney Transplant Recipients. *Emerg Infect Dis* 2020; **26**: 1329-1331 [PMID: 32441623 DOI: 10.3201/eid2606.191765]

34 **Chen S**, Sorrell T, Nimmo G, Speed B, Currie B, Ellis D, Marriott D, Pfeiffer T, Parr D, Byth K. Epidemiology and host- and variety-dependent characteristics of infection due to Cryptococcus neoformans in Australia and New Zealand. Australasian Cryptococcal Study Group. *Clin Infect Dis* 2000; **31**: 499-508 [PMID: 10987712 DOI: 10.1086/313992]

35 **Saha DC**, Goldman DL, Shao X, Casadevall A, Husain S, Limaye AP, Lyon M, Somani J, Pursell K, Pruett TL, Singh N. Serologic evidence for reactivation of cryptococcosis in solid-organ transplant recipients. *Clin Vaccine Immunol* 2007; **14**: 1550-1554 [PMID: 17959819 DOI: 10.1128/CVI.00242-07]

36 **Singh N**, Lortholary O, Dromer F, Alexander BD, Gupta KL, John GT, del Busto R, Klintmalm GB, Somani J, Lyon GM, Pursell K, Stosor V, Munoz P, Limaye AP, Kalil AC, Pruett TL, Garcia-Diaz J, Humar A, Houston S, House AA, Wray D, Orloff S, Dowdy LA, Fisher RA, Heitman J, Wagener MM, Husain S; Cryptococcal Collaborative Transplant Study Group. Central nervous system cryptococcosis in solid organ transplant recipients: clinical relevance of abnormal neuroimaging findings. *Transplantation* 2008; **86**: 647-651 [PMID: 18791444 DOI: 10.1097/TP.0b013e3181814e76]

37 **Singh N**, Dromer F, Perfect JR, Lortholary O. Cryptococcosis in solid organ transplant recipients: current state of the science. *Clin Infect Dis* 2008; **47**: 1321-1327 [PMID: 18840080 DOI: 10.1086/592690]

38 **Singh PK**, Kodati R, Rohilla M, Sharma P. Hemophagocytic lymphohistiocytosis: a rare association with pulmonary cryptococcosis. *BMJ Case Rep* 2019; **12** [PMID: 31401574 DOI: 10.1136/bcr-2019-230255]

39 **Chakradeo K**, Paul Chia YY, Liu C, Mudge DW, De Silva J. Disseminated cryptococcosis presenting initially as lower limb cellulitis in a renal transplant recipient - a case report. *BMC Nephrol* 2018; **19**: 18 [PMID: 29374464 DOI: 10.1186/s12882-018-0815-7]

40 **Muranda AZ**, Greeff L, Sathekge MM, Lengano T, Karusseit VOL. Cryptococcoma of a transplanted kidney in a patient presenting with recurrent urinary tract infection: a case report. *BMC Nephrol* 2018; **19**: 94 [PMID: 29688849 DOI: 10.1186/s12882-018-0891-8]

41 **Sandhu J**, Sandhu JS, Kaur Puri H, Munjal M. Laryngeal cryptococcus: a rare cause of hoarseness in renal allograft recipient. *J Nephropharmacol* 2017; **6**: 27-29 [PMID: 28197527 DOI: 10.4103/0971-4065.116333]

42 **Hellman RN**, Hinrichs J, Sicard G, Hoover R, Golden P, Hoffsten P. Cryptococcal pyelonephritis and disseminated cryptococcosis in a renal transplant recipient. *Arch Intern Med* 1981; **141**: 128-130 [PMID: 7004368 DOI: 10.1001/archinte.1981.00340010120023]

43 **Duarte SBL**, Oshima MM, Mesquita JVDA, do Nascimento FBP, de Azevedo PC, Reis F. Magnetic resonance imaging findings in central nervous system cryptococcosis: comparison between immunocompetent and immunocompromised patients. *Radiol Bras* 2017; **50**: 359-365 [PMID: 29307925 DOI: 10.1590/0100-3984.2016.0017]

44 **Abassi M**, Boulware DR, Rhein J. Cryptococcal Meningitis: Diagnosis and Management Update. *Curr Trop Med Rep* 2015; **2**: 90-99 [PMID: 26279970 DOI: 10.1007/s40475-015-0046-y]

45 **Birkhead M**, Naicker SD, Blasich NP, Rukasha I, Thomas J, Sriruttan C, Abrahams S, Mavuso GS, Govender NP. Cryptococcus neoformans: Diagnostic Dilemmas, Electron Microscopy and Capsular Variants. *Trop Med Infect Dis* 2018; **4** [PMID: 30577542 DOI: 10.3390/tropicalmed4010001]

46 **Liu L**, Du L, He S, Sun T, Kong F, Liu Y, Xu Y. Subculturing and Gram staining of blood cultures flagged negative by the BACTEC™ FX system: Optimizing the workflow for detection of Cryptococcus neoformans in clinical specimens. *Front Microbiol* 2023; **14**: 1113817 [PMID: 37007533 DOI: 10.3389/fmicb.2023.1113817]

47 **Shibuya K**, Coulson WF, Wollman JS, Wakayama M, Ando T, Oharaseki T, Takahashi K, Naoe S. Histopathology of cryptococcosis and other fungal infections in patients with acquired immunodeficiency syndrome. *Int J Infect Dis* 2001; **5**: 78-85 [PMID: 11468102 DOI: 10.1016/S1201-9712(01)90030-X]

48 **Dominic RS**, Prashanth H, Shenoy S, Baliga S. Diagnostic value of latex agglutination in cryptococcal meningitis. *J Lab Physicians* 2009; **1**: 67-68 [PMID: 21938253 DOI: 10.4103/0974-2727.59702]

49 **Martins Mdos A**, Brighente KB, Matos TA, Vidal JE, Hipólito DD, Pereira-Chioccola VL. Molecular diagnosis of cryptococcal meningitis in cerebrospinal fluid: comparison of primer sets for Cryptococcus neoformans and Cryptococcus gattii species complex. *Braz J Infect Dis* 2015; **19**: 62-67 [PMID: 25523072 DOI: 10.1016/j.bjid.2014.09.004]

50 **Baddley JW**, Forrest GN; AST Infectious Diseases Community of Practice. Cryptococcosis in solid organ transplantation-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 2019; **33**: e13543 [PMID: 30900315 DOI: 10.1111/ctr.13543]

51 **van der Horst CM**, Saag MS, Cloud GA, Hamill RJ, Graybill JR, Sobel JD, Johnson PC, Tuazon CU, Kerkering T, Moskovitz BL, Powderly WG, Dismukes WE. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. *N Engl J Med* 1997; **337**: 15-21 [PMID: 9203426 DOI: 10.1056/NEJM199707033370103]

52 **Husain S**, Wagener MM, Singh N. Cryptococcus neoformans infection in organ transplant recipients: variables influencing clinical characteristics and outcome. *Emerg Infect Dis* 2001; **7**: 375-381 [PMID: 11384512 DOI: 10.3201/eid0703.010302]

53 **Sun HY**, Wagener MM, Singh N. Cryptococcosis in solid-organ, hematopoietic stem cell, and tissue transplant recipients: evidence-based evolving trends. *Clin Infect Dis* 2009; **48**: 1566-1576 [PMID: 19402789 DOI: 10.1086/598936]

54 **Sun HY**, Alexander BD, Huprikar S, Forrest GN, Bruno D, Lyon GM, Wray D, Johnson LB, Sifri CD, Razonable RR, Morris MI, Stosor V, Wagener MM, Singh N. Predictors of immune reconstitution syndrome in organ transplant recipients with cryptococcosis: implications for the management of immunosuppression. *Clin Infect Dis* 2015; **60**: 36-44 [PMID: 25210020 DOI: 10.1093/cid/ciu711]

55 **O'Connor L**, Livermore J, Sharp AD, Goodwin J, Gregson L, Howard SJ, Felton TW, Schwartz JA, Neely MN, Harrison TS, Perfect JR, Hope WW. Pharmacodynamics of liposomal amphotericin B and flucytosine for cryptococcal meningoencephalitis: safe and effective regimens for immunocompromised patients. *J Infect Dis* 2013; **208**: 351-361 [PMID: 23599314 DOI: 10.1093/infdis/jit164]

56 **Dromer F**, Bernede-Bauduin C, Guillemot D, Lortholary O; French Cryptococcosis Study Group. Major role for amphotericin B-flucytosine combination in severe cryptococcosis. *PLoS One* 2008; **3**: e2870 [PMID: 18682846 DOI: 10.1371/journal.pone.0002870]

57 **Dodds-Ashley E**. Management of drug and food interactions with azole antifungal agents in transplant recipients. *Pharmacotherapy* 2010; **30**: 842-854 [PMID: 20653361 DOI: 10.1592/phco.30.8.842]

58 **Thompson GR 3rd**, Rendon A, Ribeiro Dos Santos R, Queiroz-Telles F, Ostrosky-Zeichner L, Azie N, Maher R, Lee M, Kovanda L, Engelhardt M, Vazquez JA, Cornely OA, Perfect JR. Isavuconazole Treatment of Cryptococcosis and Dimorphic Mycoses. *Clin Infect Dis* 2016; **63**: 356-362 [PMID: 27169478 DOI: 10.1093/cid/ciw305]

59 **Liliang PC**, Liang CL, Chang WN, Chen HJ, Su TM, Lu K, Lu CH. Shunt surgery for hydrocephalus complicating cryptococcal meningitis in human immunodeficiency virus-negative patients. *Clin Infect Dis* 2003; **37**: 673-678 [PMID: 12942399 DOI: 10.1086/377208]

60 **Kagimu E**, Engen N, Ssebambulidde K, Kasibante J, Kiiza TK, Mpoza E, Tugume L, Nuwagira E, Nsangi L, Williams DA, Hullsiek KH, Boulware DR, Meya DB, Rhein J, Abassi M, Musubire AK. Therapeutic Lumbar Punctures in Human Immunodeficiency Virus-Associated Cryptococcal Meningitis: Should Opening Pressure Direct Management? *Open Forum Infect Dis* 2022; **9**: ofac416 [PMID: 36092828 DOI: 10.1093/ofid/ofac416]

61 **Chang CC**, Perfect JR. Repeated therapeutic lumbar punctures in cryptococcal meningitis - necessity and/or opportunity? *Curr Opin Infect Dis* 2016; **29**: 539-545 [PMID: 27607912 DOI: 10.1097/QCO.0000000000000315]

62 **Beardsley J**, Wolbers M, Kibengo FM, Ggayi AB, Kamali A, Cuc NT, Binh TQ, Chau NV, Farrar J, Merson L, Phuong L, Thwaites G, Van Kinh N, Thuy PT, Chierakul W, Siriboon S, Thiansukhon E, Onsanit S, Supphamongkholchaikul W, Chan AK, Heyderman R, Mwinjiwa E, van Oosterhout JJ, Imran D, Basri H, Mayxay M, Dance D, Phimmasone P, Rattanavong S, Lalloo DG, Day JN; CryptoDex Investigators. Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis. *N Engl J Med* 2016; **374**: 542-554 [PMID: 26863355 DOI: 10.1056/NEJMoa1509024]

63 **Panackal AA**, Marr KA, Williamson PR. Dexamethasone in Cryptococcal Meningitis. *N Engl J Med* 2016; **375**: 188 [PMID: 27410935 DOI: 10.1056/NEJMc1605205]

64 **Singh N**, Perfect JR. Immune reconstitution syndrome associated with opportunistic mycoses. *Lancet Infect Dis* 2007; **7**: 395-401 [PMID: 17521592 DOI: 10.1016/S1473-3099(07)70085-3]

65 **Ponzio V**, Camargo LF, Medina-Pestana J, Perfect JR, Colombo AL. Outcomes of cryptococcosis in renal transplant recipients in a less-resourced health care system. *Transpl Infect Dis* 2018; **20**: e12910 [PMID: 29677399 DOI: 10.1111/tid.12910]

66 **Legris T**, Massad M, Purgus R, Vacher-Coponat H, Ranque S, Girard N, Berland Y, Moal V. Immune reconstitution inflammatory syndrome

mimicking relapsing cryptococcal meningitis in a renal transplant recipient. *Transpl Infect Dis* 2011; **13**: 303-308 [PMID: 21159113 DOI: 10.1111/j.1399-3062.2010.00592.x]

67 **Wiesner DL**, Boulware DR. Cryptococcus-Related Immune Reconstitution Inflammatory Syndrome(IRIS): Pathogenesis and Its Clinical Implications. *Curr Fungal Infect Rep* 2011; **5**: 252-261 [PMID: 22389746 DOI: 10.1007/s12281-011-0064-8]

68 **Cruz MC**, Del Poeta M, Wang P, Wenger R, Zenke G, Quesniaux VF, Movva NR, Perfect JR, Cardenas ME, Heitman J. Immunosuppressive and nonimmunosuppressive cyclosporine analogs are toxic to the opportunistic fungal pathogen Cryptococcus neoformans *via* cyclophilin-dependent inhibition of calcineurin. *Antimicrob Agents Chemother* 2000; **44**: 143-149 [PMID: 10602736 DOI: 10.1128/AAC.44.1.143-149.2000]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Effectiveness and safety of apixaban and rivaroxaban *vs* warfarin in patients with atrial fibrillation and chronic kidney disease

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Abstract

BACKGROUND

Randomized controlled trials (RCTs) of direct oral anticoagulants (DOACs) included a low proportion of atrial fibrillation (AF) patients with chronic kidney disease (CKD), and suggested that DOACs are safe and effective in patients with mild-to-moderate CKD. In a metanalysis of RCTs and observational studies, DOACs were associated with better efficacy (*vs* warfarin) in early CKD and had similar efficacy and safety profiles in patients with stages IV-V CKD. But few studies have provided data on the safety and effectiveness of each DOAC *vs* warfarin in patients with stage III CKD. The effectiveness and safety of DOACs in those patients are still subject to debate.

AIM

To assess and compare the effectiveness and safety of apixaban and rivaroxaban *vs* warfarin in this patient population.

METHODS
A cohort of patients with an inpatient or outpatient code for AF and stage III CKD who were newly prescribed apixaban and rivaroxaban was created using the administrative databases from the Quebec province of Canada between 2013 and 2017. The primary effectiveness outcome was a composite of ischemic stroke, systemic embolism, and death, whereas the primary safety outcome was a composite of major bleeding within a year of DOAC *vs* warfarin initiation. Treatment groups were compared in an under-treatment analysis using inverse probability of treatment weighting and Cox proportional hazards.

RESULTS
A total of 8899 included patients filled out a new oral anticoagulation therapy claim; 3335 for warfarin and 5564 for DOACs. Compared with warfarin, 15 mg and 20 mg rivaroxaban presented a similar effectiveness and safety composite risk. Apixaban 5.0 mg was associated with a lower effectiveness composite risk [Hazard ratio (HR) 0.76; 95% confidence interval (CI): 0.65-0.88] and a similar safety risk (HR 0.94; 95%CI: 0.66-1.35). Apixaban 2.5 mg was associated with a similar effectiveness composite (HR 1.00; 95%CI: 0.79-1.26) and a lower safety risk (HR 0.65; 95%CI: 0.43-0.99. Although, apixaban 5.0 mg was associated with a better effectiveness (HR 0.76; 95%CI: 0.65-0.88), but a similar safety risk profile (HR 0.94; 95%CI: 0.66-1.35). The observed improvement in the effectiveness composite for apixaban 5.0 mg was driven by a reduction in mortality (HR 0.61; 95%CI: 0.43-0.88).

CONCLUSION
In comparison with warfarin, rivaroxaban and apixaban appear to be effective and safe in AF patients with stage III CKD.

Key Words: Atrial fibrillation; Chronic kidney disease; Direct oral anticoagulant; Effectiveness; Safety; Warfarin

Core Tip: Compared to warfarin, rivaroxaban and apixaban appear to be effective and safe in atrial fibrillation patients with stage III chronic kidney disease (CKD) in real world. Rivaroxaban 15 mg and 20 mg presented a similar effectiveness and safety composite risk. However, apixaban 2.5 mg might even have a better safety profile than warfarin, while apixaban 5.0 mg might have a better effectiveness profile than warfarin, to a reduction in deaths. Appropriately sized randomized controlled trials are needed to confirm these findings in stage III CKD patients.

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INTRODUCTION

Patients with chronic kidney disease (CKD) often develop atrial fibrillation (AF) at a rate of more than twice that of the general population[1-3]. Because patients with both AF and CKD have a greater risk of systemic embolism and bleeding events, an effective therapy is challenging[4-6]. For patients with non-valvular AF (NVAF) requiring oral anticoagulation therapy (OAC), medical evidence suggests treatment with a direct oral anticoagulant (DOAC) over warfarin , including patients with stage I-IV CKD[7]. Despite these recommendations, warfarin remains the OAC of choice for most AF patients [8] as well as AF patients with moderate to severe CKD[9].

Although the randomized controlled trials (RCTs) of DOACs included a low proportion of AF patients with CKD, the results suggested that DOACs are safe and effective in patients with mild-to-moderate CKD (stages I-III CKD, using Cockcroft-Cault formula)[10-13]. In a metanalysis of observational studies and RCTs, DOACs were found to be more effective (*vs* warfarin) in early CKD and had similar efficacy and safety profiles in patients with CKD stages IV-V as well as patients on dialysis[14]. Recent population-based studies of AF patients with CKD have also examined the effectiveness and safety of DOACs *vs* warfarin[15-22]. However, few of these studies examined the safety and effectiveness of individual DOACs *vs* warfarin, nor did they examine the impact of varying doses in patients with stage III CKD with respect to stroke, systemic embolic events, major bleeding, or death[16,23]. Therefore, we attempted to evaluate and compare the efficacy and safety of various DOACs, including low-dose rivaroxaban (15 mg once per day), standard-dose rivaroxaban (20 mg once per day), low-dose apixaban (2.5 mg twice per day), and standard-dose apixaban (5.0 mg twice per day) *vs* warfarin in AF patients with stage III CKD.

MATERIALS AND METHODS

We analyzed several Quebec health care claims databases, in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[24]. The need for informed consent was waived by the local institutional research committee (University of Montreal, Montreal, Quebec, Canada). The study protocol complied with the ethical guidelines of the 1975 declaration of Helsinki and was approved by the institutional research committee of the University of Montreal.

Data sources

We assembled a cohort of inpatients or outpatients using the Med-Echo administrative databases (hospital discharge reports), medical services of the Régie de l'Assurance Maladie du Québec (RAMQ), and RAMQ public drug plans, all databases administered by the RAMQ[25-28]. The databases were linked *via* encrypted health insurance numbers. Information from these databases provided a complete picture of hospital admissions, medical services, and medication used, if the patient was still living in the Quebec province.

Population

We identified adult patients with AF from January 1, 2013, to December 31, 2017. AF was detected by searching for the international classification of diseases, 9th revision (ICD-9) codes 427.3, 427.31, or 427.32, or the international classification of diseases, 10th revision (ICD-10) code I48[29,30]. The first instance of AF coding was used to determine eligibility. The cohort was subsequently restricted to patients who filled a new prescription for rivaroxaban (15 mg or 20 mg once daily), apixaban (2.5 or 5.0 mg twice daily) or warfarin within a year of AF diagnosis. Few patients had a new prescription of either dabigatran or edoxaban, so they were not included in our analysis. The date of the first OAC claim was defined as the date of cohort entry. New OAC users were defined as those not exposed to any OACs in the year prior to the claim index date. Patients were also required to have had pharmacy coverage for at least 12 mo and enrollment in a drug health insurance plan for at least one year before cohort entry.

We also excluded patients with a code for any condition or procedure that might have impacted the choice of OAC and duration of treatment at discharge: Cardiac valve replacement or valve procedures in the five years before cohort entry; end-stage CKD (meaning being on dialysis), kidney transplant, dialysis, or coagulation deficiency in the three years before cohort entry; medical procedures (including cardiac catheterization, stent, coronary artery bypass grafting, cerebrovascular, or defibrillator) in the three months before cohort entry; deep vein thrombosis or orthopedic surgery in the six months before cohort entry.

Lastly, the cohort was restricted to patients with stage III CKD by using the algorithm 2 to identify CKD G3-5ND, and then applying the exclusion of CKD G4-5ND by using the algorithm 3 (as defined by a composite variable covering the ICD code, drug use, and consultations with a nephrologist, as identified in the administrative databases). The composite variable has been validated, with reference to medical chart reviews of older adults with CKD [the algorithm used for estimated glomerular filtration rate (eGFR) definition], and has presented good positive predictive values[31].

Exposure

Treatment with an OAC was checked against the prescription fulfillment dates and the number of days of medication supplied for each fill. Exposure to treatment was considered in all analyses. We consider a gap of less than 30 d between the end of a treatment period and a new fill corresponded to continuous treatment. Patients were censored when they discontinued a treatment, switched to another OAC, or to another dose level. Allowing a gap in treatment of up to 30 d is reasonable because of the DOACs' short half-life. Taking this definition into account, the adherence rate over the 12-mo assessment period was at least 92% for all included patients. The patient's OAC exposure and censored status were updated every 30 d.

Outcomes

The primary effectiveness outcome was a composite of ischemic stroke or systemic embolism (SE) and all-cause mortality. The primary safety outcome was a composite of major bleeding, defined as either intracranial hemorrhage, gastrointestinal bleeding, or major bleeding from other sites. The individual components of the safety and effectiveness outcomes were evaluated in a secondary analysis.

We identified the outcomes by screening the ICD-9 or ICD-10 codes for the primary diagnosis on inpatient claims (Supplementary Table 1). In earlier validation studies, these codes performed relatively well and gave positive predictive values of over 80%[32,33].

Patient demographics and clinical characteristics

We documented demographic variables upon cohort entry and determined the associated morbidities from the inpatient and outpatient ICD-9 and ICD-10 diagnostic codes recorded in the three years preceding the cohort entry[30-32]. Next, we used the patients' characteristics and associated comorbidities to calculate the $CHADS_2$ score (Supplementary Tables 2 and 3)[34] and the modified HAS-BLED score (Supplementary Tables 2 and 4). The comorbidity burden was scored with the Charlson-Deyo Comorbidity Index[35,36]. A frailty score was also calculated from the modified elders risk assessment in the two years preceding cohort entry[37,38]. Lastly, we assessed all drug prescriptions filled in the two weeks preceding the cohort entry.

Statistical analyses

Descriptive statistics were used to summarize the demographic and clinical characteristics of patients, according to the type of OAC used. The follow-up periods and the level of adherence were reported as the mean with standard deviation (SD) or the median with interquartile range. The adherence to treatment in the year of follow-up was calculated by dividing the total number of days of treatment by 365. When the dispensing periods overlapped, the full length of each filled claim was accounted for, and the start date of the second claim was shifted to the end of the previous claim.

For the main analyses of the primary effectiveness and safety composites in an on-treatment, we used an inverse probability of treatment weighting (IPTW) approach to account for differences in patient characteristics between treatment groups[39,40]. Four IPTW cohorts were created: (1) Rivaroxaban 15 mg *vs* warfarin; (2) rivaroxaban 20 mg *vs* warfarin; (3) apixaban 2.5 mg *vs* warfarin; and (4) apixaban 5.0 mg *vs* warfarin. We then used a multivariable logistic regression model to estimate the observed probability (according to propensity score matching) of being in the treatment group (rivaroxaban 15 mg, rivaroxaban 20 mg, apixaban 2.5 mg, and apixaban 5.0 mg), based on all the baseline covariates, and the impact of temporal trends accounted for in the analysis by including the date of cohort entry in the IPTW matching. By approximating the randomization used in RCTs, the IPTW approach establishes a pseudo-population, balances the treatment groups according to the covariates included in the model, and thus minimizes the impact of confounding biases in observational studies. All weights were stabilized by multiplying the IPTW weight by the marginal probability of being in the treatment group. Descriptive statistics were also used to summarize the baseline characteristics of each IPTW cohort. For baseline characteristics, only absolute standardized differences of 10% or more between the unadjusted cohort and the IPTW-adjusted cohort were considered meaningful[39]. We reported the outcomes per 100 person-years for each treatment in each IPTW population. Hazard ratios (HRs) with 95%CIs associated were estimated using Cox proportional hazards models for each of the four IPTW cohorts described above.

Patients were censored at the time of enrollment if they were in a non-governmental drug coverage plan, admitted to a long-term care facility, admitted to the hospital (for more than two weeks), or in the case of a safety or effectiveness endpoint or death (whichever occurred first). The patient's OAC exposure and censored status were updated every 30 d.

For the sensitivity analyses of the primary effectiveness and safety composites, we first estimated Cox proportional HRs for outcomes in an intent-to-treat analyses in which we removed the censoring criteria of drug discontinuation or switching, so that all patients were followed up for 365 d unless they were censored for another reason. We used an IPTW approach to account for differences in patient characteristics between treatment groups. We reported the outcomes per 100 person-years for each treatment in each IPTW population. HRs and 95%CIs associated were estimated using Cox proportional hazards models for each of the four IPTW cohorts described above.

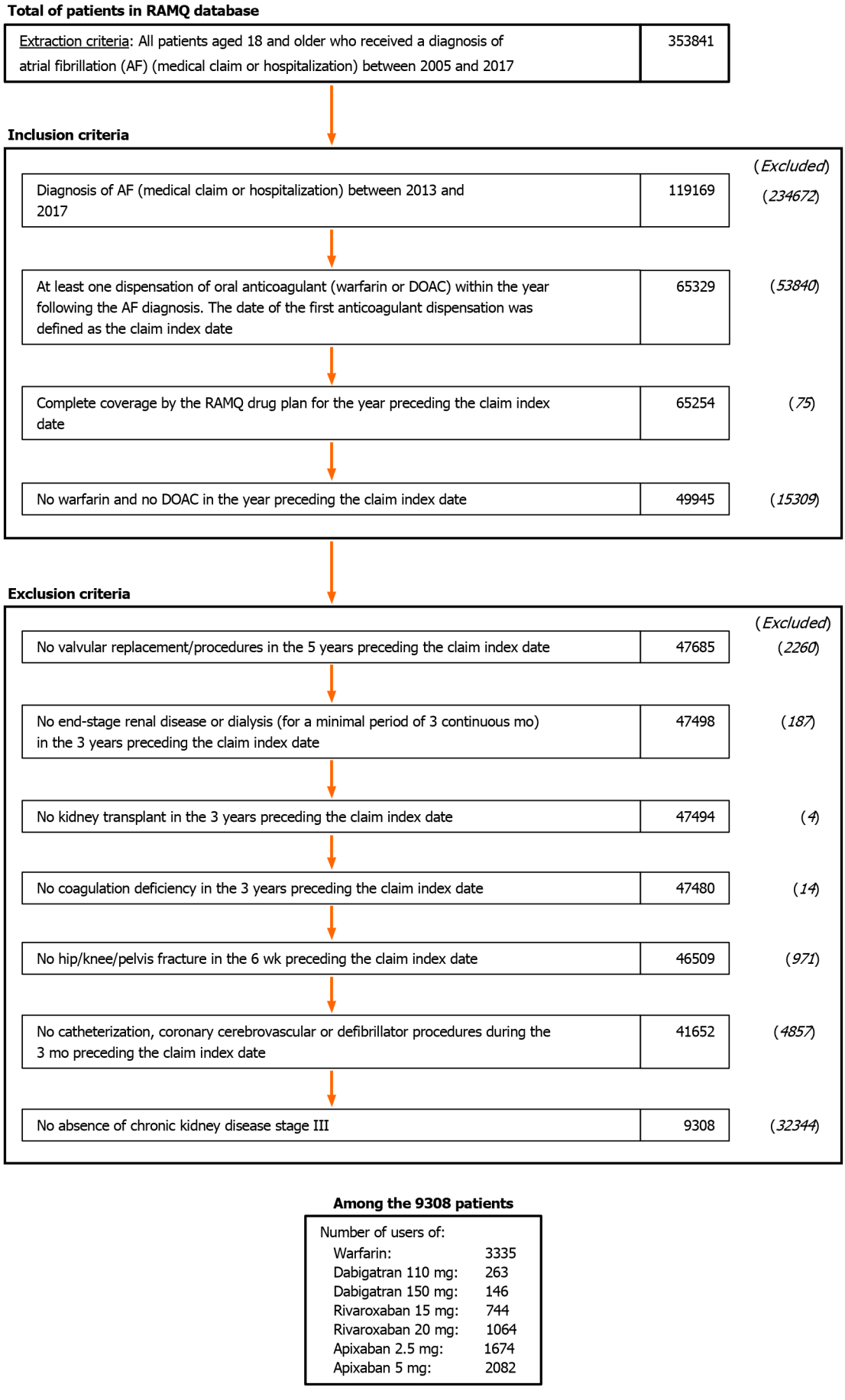
Secondly, we provided a negative control outcomes analyses using the risk of diabetes complications (primary code of hospitalization (ICD-9: 250.1-250.9, 357.2, 366.41; ICD-10: E10-E14 excluding E10.9, E11.9, E12.9, E13.0, E14.9). Lastly, we calculated an E-value to assess the impact of unmeasured confounding[41]. The E-value indicates how strongly an unmeasured confounder would have to be associated with use of apixaban 2.5 mg, or apixaban 5.0 mg *vs* warfarin and the outcomes to reduce the observed effect to the null, depending on the measured covariates. All analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC). A biomedical statistician performed statistical review of the study.

RESULTS

A total of 8899 included AF patients with stage III CKD filled a new OAC prescription: 3335 for warfarin, 744 for the 15-mg dose of rivaroxaban, 1064 for 20-mg rivaroxaban, 1674 for 2.5-mg apixaban, and 2082 for 5.0-mg apixaban (Figure 1). The frequency of warfarin prescriptions decreased over time and was associated with a concomitant increase in DOAC prescription (Figure 2). As of 2017, apixaban 5.0 mg was the most commonly initiated drug.

Demographic and clinical characteristics

The patients' unadjusted characteristics are summarized in Supplementary Tables 5-8. Compared with warfarin users, rivaroxaban 15 mg users were slightly younger (mean ± SD age: 83.0 ± 8.5 *vs* 82.6 ± 7.8, respectively) and had a lower mean ± SD Charlson-Deyo Comorbidity index (6.1 ± 3.4 *vs* 5.3 ± 3.5, respectively), a lower mean ± SD $CHADS_2$ score (3.1 ± 1.2 *vs* 2.8 ± 1.2, respectively) and a lower mean ± SD HAS-BLED score of 3.6 ± 1.3 *vs* 3.2 ± 1.3, respectively. Compared with users of warfarin, rivaroxaban 20 mg users were younger (mean ± SD age: 83.0 ± 8.5 *vs* 74.2 ± 9.2, respectively) and had a lower mean ± SD Charlson-Deyo Comorbidity index (6.1 ± 3.4 *vs* 4.7 ± 3.5, respectively), a lower mean ± SD $CHADS_2$ score (3.1 ± 1.2 *vs* 2.3 ± 1.2, respectively), and a lower mean ± SD HAS-BLED score (3.6 ± 1.3 *vs* 2.7 ± 1.3, respectively). Compared with warfarin users, apixaban 2.5 mg users were older (mean ± SD age: 83.0 ± 8.5 *vs* 86.5 ± 6.3, respectively), had a lower mean ± SD Charlson-Deyo Comorbidity index (6.1 ± 3.4 *vs* 5.4 ± 3.3, respectively), a similar mean ± SD $CHADS_2$ score of 3.1 ± 1.2 *vs* 3.0 ± 1.1, respectively), and a similar mean ± SD HAS-BLED score of 3.6 ± 1.3 *vs* 3.3 ± 1.3, respectively. And, compared with users of warfarin, apixaban 5.0 mg users were also younger (mean ± SD age: 83.0 ± 8.5 *vs* 78.0 ± 8.4, respectively), and had a lower mean ± SD Charlson-Deyo Comorbidity index (6.1 ± 3.4 *vs* 5.1 ± 3.5, respectively), a lower mean ± SD $CHADS_2$ score (3.1 ± 1.2 *vs* 2.6 ± 1.2, respectively), and a lower mean ± SD HAS-BLED score (3.6 ± 1.3 *vs* 3.0 ± 1.3, respectively). As shown in Table 1, demographic and clinical characteristics of cohorts of new OAC users with stage III CKD after IPTW from 2013 to 2017 are well balanced.


Total of patients in RAMQ database
Extraction criteria: All patients aged 18 and older who received a diagnosis of atrial fibrillation (AF) (medical claim or hospitalization) between 2005 and 2017
353841
Inclusion criteria
(Excluded)
Diagnosis of AF (medical claim or hospitalization) between 2013 and 2017
119169
(234672)
At least one dispensation of oral anticoagulant (warfarin or DOAC) within the year following the AF diagnosis. The date of the first anticoagulant dispensation was defined as the claim index date
65329
(53840)
Complete coverage by the RAMQ drug plan for the year preceding the claim index date
65254
(75)
No warfarin and no DOAC in the year preceding the claim index date
49945
(15309)
Exclusion criteria
(Excluded)
No valvular replacement/procedures in the 5 years preceding the claim index date
47685
(2260)
No end-stage renal disease or dialysis (for a minimal period of 3 continuous mo) in the 3 years preceding the claim index date
47498
(187)
No kidney transplant in the 3 years preceding the claim index date
47494
(4)
No coagulation deficiency in the 3 years preceding the claim index date
47480
(14)
No hip/knee/pelvis fracture in the 6 wk preceding the claim index date
46509
(971)
No catheterization, coronary cerebrovascular or defibrillator procedures during the 3 mo preceding the claim index date
41652
(4857)
No absence of chronic kidney disease stage III
9308
(32344)
Among the 9308 patients
Number of users of:
Warfarin: 3335
Dabigatran 110 mg: 263
Dabigatran 150 mg: 146
Rivaroxaban 15 mg: 744
Rivaroxaban 20 mg: 1064
Apixaban 2.5 mg: 1674
Apixaban 5 mg: 2082

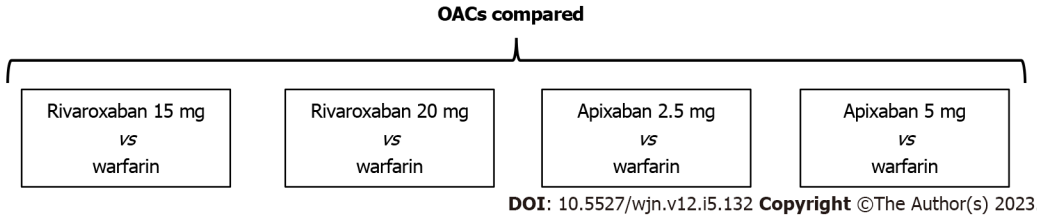


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Figure 1 Study flow chart. No patients in the cohort received edoxaban, and patients using dabigatran were excluded for the low sample size between 2011-2017. DOAC: Direct oral anticoagulant; RAMQ: Régie d'Assurance Maladie du Québec.

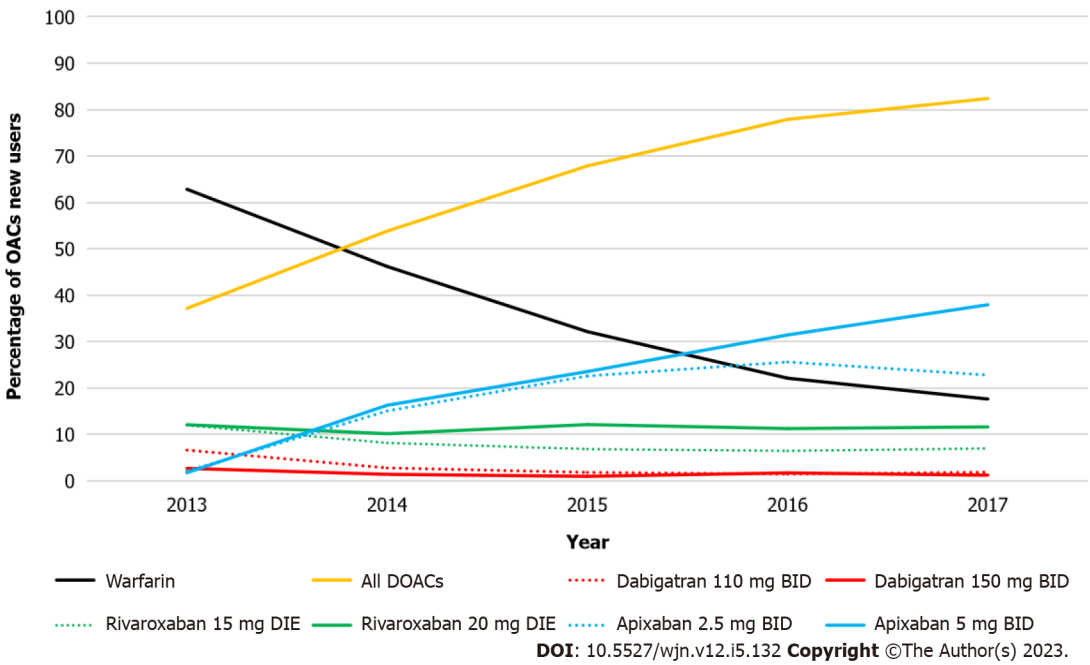

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Figure 2 Changes in oral anticoagulant prescriptions from 2010 to 2017. DOACs: Direct oral anticoagulants; OAC: Oral anticoagulant.

Cumulative incidence in the IPTW cohorts

As shown in Table 1 and Supplementary Tables 5-8, there were no significant differences in baseline characteristics between the IPTW treatment groups. In Figures 3 and 4, we show the cumulative incidence curves for the effectiveness and safety composite outcomes in the IPTW in an on-treatment analysis. The follow-up times and levels of adherence are shown in Supplementary Tables 9 and 10.

HRs for effectiveness and safety outcomes in the IPTW cohorts

The annual rates and HRs for the primary analyses of the safety and effectiveness composites in the IPTW treatment groups in an on-treatment are shown in Supplementary Table 11. With warfarin as the reference group, we found rivaroxaban 15 mg and 20 mg had a similar effectiveness composite (HR 0.84; 95%CI: 0.60-1.18 and HR 0.83; 95%CI: 0.61-1.13, respectively) (Figure 5); and similar safety profile (HR 1.13; 95%CI: 0.70-1.83 and HR 1.29; 95%CI: 0.84-1.95, respectively). Apixaban 2.5 mg was similarly effective (HR 1.00; 95%CI: 0.79-1.26), but had a better safety profile (HR 0.65; 95%CI: 0.43-0.99), while apixaban 5.0 mg was associated with a better effectiveness (HR 0.76; 95%CI: 0.65-0.88), but a similar safety profile (HR 0.94; 95%CI: 0.66-1.35). A reduction in mortality (HR 0.61; 95%CI: 0.43-0.88) accounted for the observed improvement in the effectiveness composite for apixaban 5.0 mg.

Sensitivity analyses

The annual rates and HRs for the analyses of the effectiveness and safety composites in the IPTW treatment groups in an intent-to-treat are shown in Supplementary Table 12. Under intent-to-treat analyses, rivaroxaban 20 mg presented a better effectiveness composite (HR 0.79; 95%CI: 0.65-0.96), and the observed improvement in the effectiveness composite was due to a reduction in mortality (HR 0.72; 95%CI: 0.58-0.91) (Figure 6). Those point estimates are in relation to those observed in the IPTW treatment groups in an on-treatment, and the level of significance is linked to an increase of the number of events, particularly among those in the warfarin group.

As shown in Table 2, warfarin and DOACs had a similar rate of hospitalization per 100 person-years for diabetes complications, with no significant HRs. As we expected, all groups had similar results. In Table 3, we found the E-value closest to boundary 1 for the effectiveness composite and apixaban 5.0 mg *vs* warfarin was 1.53; hence, we suspect an

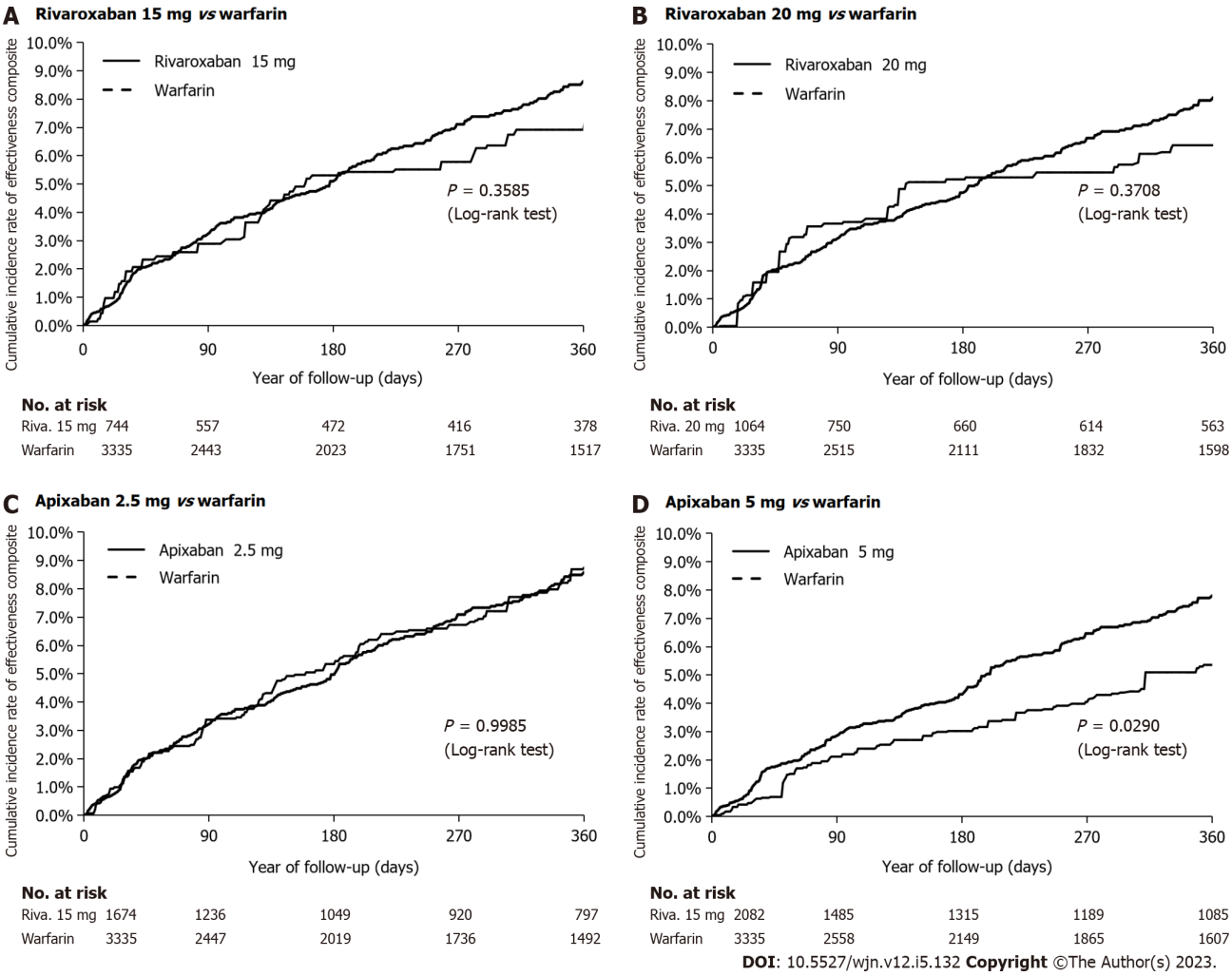

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Figure 3 Cumulative rate of the primary effectiveness outcome after inverse probability of treatment weighting in an on-treatment analysis. A: Rivaroxaban 15 mg *vs* warfarin; B: Rivaroxaban 20 mg *vs* warfarin; C: Apixaban 2.5 mg *vs* warfarin; D: Apixaban 5 mg *vs* warfarin.

unmeasured confounder occurring 1.53 times more frequently in patients receiving apixaban 5.0 mg than in patients receiving warfarin, thus increasing the rate of safety composite events by a factor of 1.53. The high E-values indicate that the statistically significant results are robust with regards to unmeasured confounding factors.

DISCUSSION

The results of our cohort analysis provided several insights relevant to clinical practice. Firstly, DOAC prescription increased substantially over time, whereas warfarin prescription fell concomitantly. Nevertheless, over 10% of AF patients with stage III CKD were still being prescribed warfarin in 2017. Secondly, relative to warfarin, rivaroxaban appears to be safe and effective in AF patients with stage III CKD. Apixaban 2.5 mg might even have better safety profiles than warfarin; and for apixaban 5.0 mg, this difference in effectiveness was mainly driven by a reduction in deaths.

The increase in DOAC prescription is in line with the latest AF guidelines from the Canadian society of cardiology and European society of cardiology, which recommend DOAC therapy over warfarin for patients with NVAF and stage III CKD[7,42]. This recommendation is based on a sub-analysis of AF RCTs, which demonstrated that along with the DOACs' logistic advantages *vs* dose-adjusted warfarin, these drugs are no worse or even better than warfarin for reducing the risk of AF-associated stroke or SE in AF patients with stage III CKD, with a lower or similar major bleeding risk[10-13]. A meta-analysis of RCTs and observational trials of AF patients with CKD showed that DOACs can provide a significant reduction in stroke/SE (HR 0.81; 95%CI: 0.68-0.97) and a nonsignificant reduction in major bleeding (HR 0.87; 95%CI: 0.69-1.05) in stage III CKD, when compared with warfarin[14].

Very little data exists regarding the effectiveness and safety of individual DOACs and the impact of various doses on patients with stage III CKD. Most of the existing data comes from observational studies[15-21]. Data from a sub-analysis of the Aristotle trial demonstrated that apixaban can effectively reduce the occurence of stroke, major bleeding, and mortality compared to that of warfarin among patients with impaired renal function (≤ 50 mL/min), when using creatinine-based estimates of GFR[13]. Wetmore *et al*[23] examined Medicare data from 22739 AF patients with stage III-

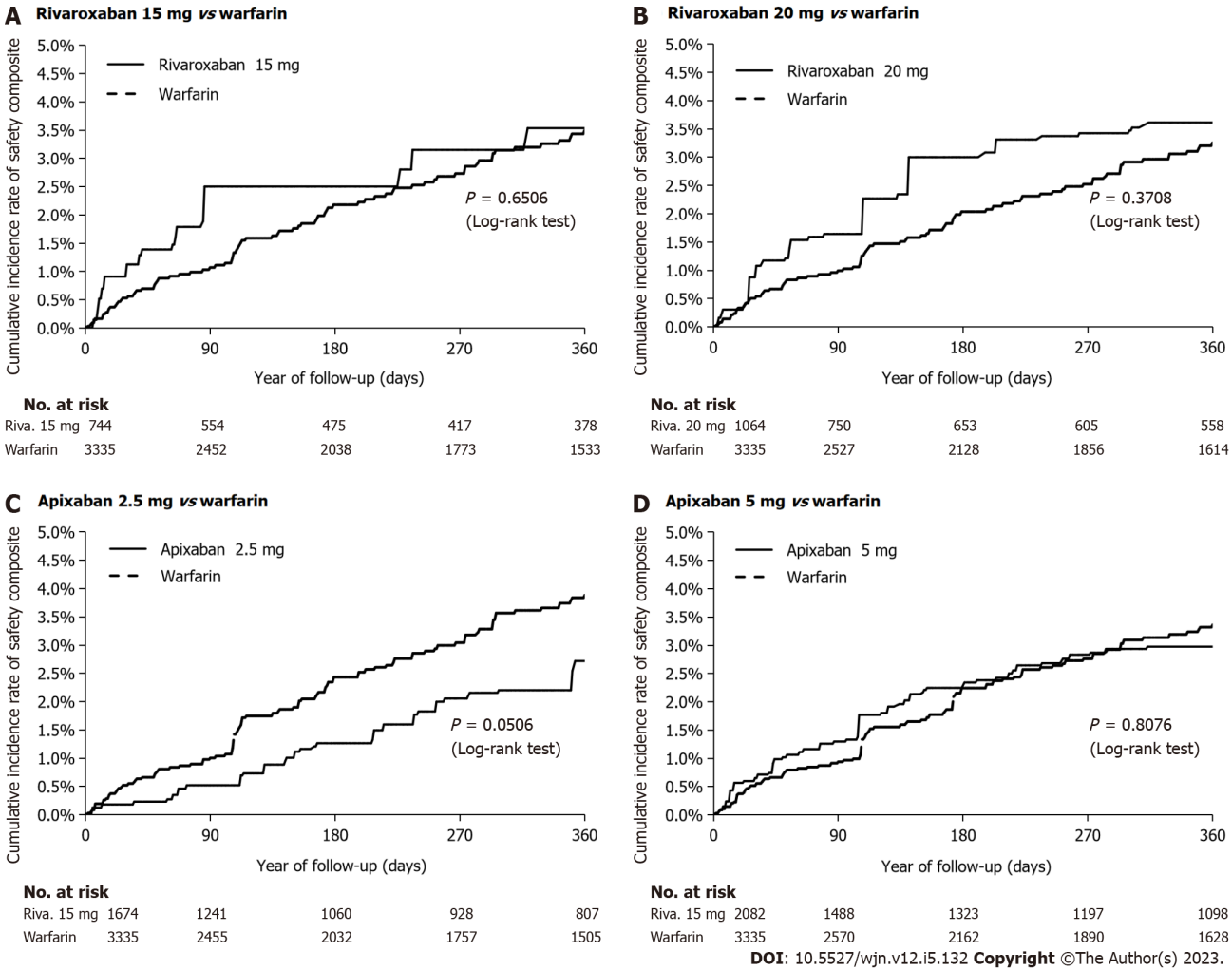

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Figure 4 Cumulative rate of the primary safety outcome after inverse probability of treatment weighting in an on-treatment analysis. A: Rivaroxaban 15 mg *vs* warfarin; B: Rivaroxaban 20 mg *vs* warfarin; C: Apixaban 2.5 mg *vs* warfarin; D: Apixaban 5 mg *vs* warfarin.

IV CKD and found that apixaban reduced stroke/SE (HR 0.70; 95%CI: 0.51-0.96) and risk of major bleeding (HR 0.47; 95%CI: 0.37-0.59). Using electronic health record data, Fu *et al*[43] examined the safety and effectiveness of rivaroxaban *vs* warfarin in 555 stage III CKD AF patients and found a similar risk of stroke (HR 0.60; 95%CI: 0.23-1.56) and major bleeding (HR 0.73; 95%CI: 0.38-1.41). A subanalysis of the ROCKET-AF trial found that rivaroxaban 20 mg daily had a better efficacy profile in patients with a creatinine clearance (CrCl) of 50 mL/min or more but that rivaroxaban 15 mg daily had a similar efficacy profile in patients with a CrCl of 30-49 mL/min; the safety profile was similar for both CrCl categories[44]. Nonetheless, dose adjustment yielded results consistent with the overall trial, when compared with dose-adjusted warfarin[11]. Wetmore *et al*[23] found that in AF patients with stage III-IV CKD, rivaroxaban was associated with similar risks of stroke/SE (HR 0.80; 95%CI: 0.54-1.17) and major bleeding (HR 1.05; 95%CI: 0.85-1.30). However, the investigators did not report data on the effectiveness and safety of each dose level of DOAC *vs* warfarin in stage III CKD AF patients specifically.

Likewise, very few published studies have examined the impact of DOAC therapy *vs* warfarin on mortality, and also per specific dose. Makani *et al*[17] examined electronic health record data on 21733 AF patients with CKD and found that DOACs reduce the risk of all-cause mortality for all CKD classes. When examining individual DOACs in an on-treatment analysis, Wetmore *et al*[23] found a reduction in mortality for apixaban (HR 0.90; 95%CI: 0.84-0.96) but not for rivaroxaban (HR 0.95; 95%CI: 0.88-1.02) or dabigatran (HR 0.92; 95%CI: 0.84-1.01). These results might be explained by the fact that DOACs are associated with a lower incidence of renal adverse outcomes in patients with mild-to-moderate CKD, including declined renal function, a doubling in the serum creatinine level, or acute kidney injury[45]. Moreover, warfarin treatment is associated with an elevated risk of vascular and cardiac valve calcification[46-48], which in turn is associated with greater cardiovascular morbidity and mortality rates[49].

The present study has several strengths. First, it is one of the few large, real-world comparative studies of the effectiveness, safety, and mortality rates associated with individual DOACs and their dose levels *vs* warfarin. Second, we analyzed the single-payer health care claims database across the province of Quebec. Given that: (1) Most such clinical events result in an administrative claim, and (2) few patients in the province travel outside of Quebec for medical treatment, the study may likely have captured the vast majority of clinically significant events; which might not have been the case in previous single-hospital or single-insurer studies. Third, we performed IPTW cohorts by accounting for

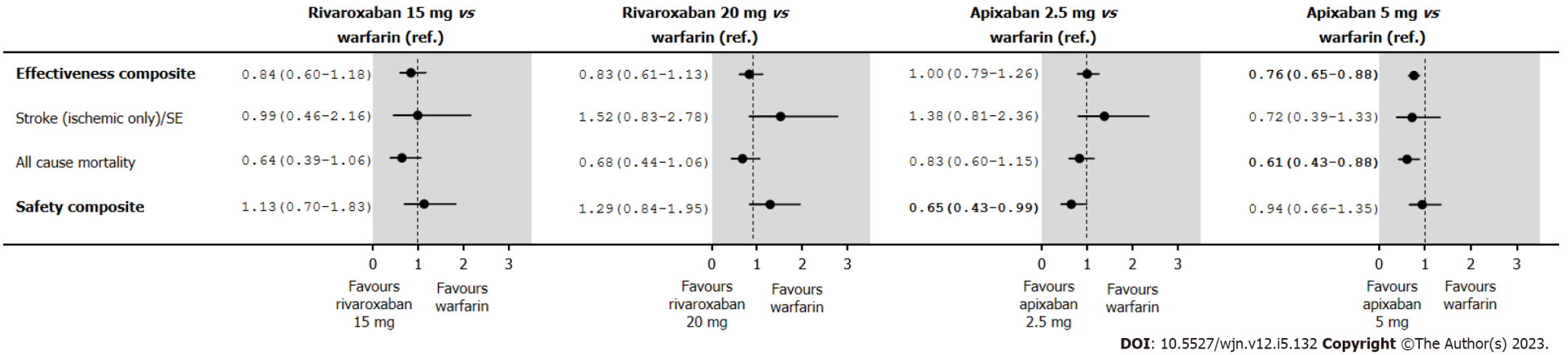

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Figure 5 Hazard ratios (95% confidence interval) of effectiveness and safety outcomes in an on-treatment after inverse probability of treatment weighting of new oral anticoagulant users with stage III chronic kidney disease. SE: Systemic embolism.

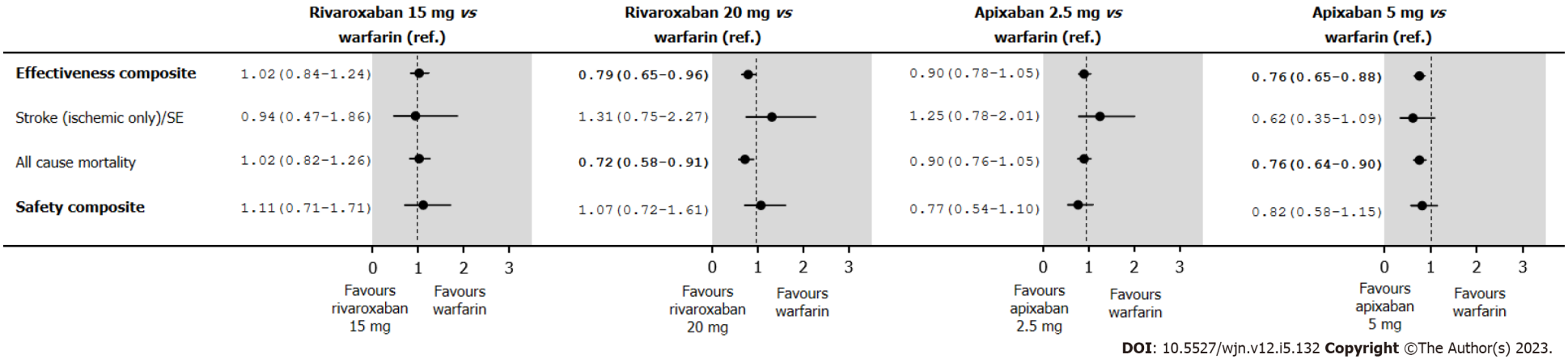

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Figure 6 Hazard ratios (95% confidence interval) of effectiveness and safety outcomes in an intent-to-treat after inverse probability of treatment weighting of new oral anticoagulant users with stage III chronic kidney disease. SE: Systemic embolism.

Table 1 Demographic and clinical characteristics of cohorts of new oral anticoagulation therapy users with stage III chronic kidney disease after inverse probability of treatment weighting from 2013 to 2017 (mean ± SD, %)

	IPTW warfarin and rivaroxaban 15 mg		IPTW warfarin and rivaroxaban 20 mg		IPTW warfarin and apixaban 2.5 mg		IPTW warfarin and apixaban 5.0 mg	
	Warfarin (n = 3335)	Rivaroxaban 15 mg (n = 744)	Warfarin (n = 3335)	Rivaroxaban 20 mg (n = 1064)	Warfarin (n = 3335)	Apixaban 2.5 mg (n = 1674)	Warfarin (n = 3335)	Apixaban 5.0 mg (n = 2082)
Age (yr)	82.9 ± 8.6	82.8 ± 7.7	80.1 ± 10.8	79.1 ± 8.2	84.3 ± 8.3	84.5 ± 7.2	80.4 ± 10.2	80.2 ± 7.8
Female sex	56.5	56.5	54.8	52.3	58.2	59.0	54.3	53.9
CHA_2DS_2-VASc	4.1 ± 1.4	4.1 ± 1.3	3.9 ± 1.5	3.9 ± 1.5	4.2 ± 1.4	4.2 ± 1.3	3.9 ± 1.5	3.8 ± 1.3
$CHADS_2$ score	3.0 ± 1.2	3.0 ± 1.2	2.8 ± 1.3	2.9 ± 1.2	3.0 ± 1.2	3.0 ± 1.1	2.9 ± 1.3	2.8 ± 1.1
HAS-BLED score	3.5 ± 1.3	3.5 ± 1.3	3.3 ± 1.5	3.4 ± 1.4	3.5 ± 1.3	3.5 ± 1.2	3.3 ± 1.4	3.3 ± 1.2
Charlson-Deyo Comorbidity Index	5.9 ± 3.4	6.0 ± 3.6	5.7 ± 3.5	5.9 ± 3.6	5.9 ± 3.4	5.8 ± 3.2	5.7 ± 3.5	5.7 ± 3.4
Frailty score	18.6 ± 6.2	18.6 ± 5.9	17.7 ± 6.7	17.6 ± 6.3	18.8 ± 6.2	18.8 ± 5.8	17.7 ± 6.6	17.5 ± 6.1
Comorbidities (including the index hospitalization and the three years prior to cohort entry)								
Hypertension	86.2	86.5	83.9	85.2	86.9	86.9	84.5	84.0
Coronary artery disease	64.7	65.1	62.0	62.7	64.1	62.5	61.2	58.4
Acute myocardial infarction	21.1	20.3	18.9	17.5	20.9	20.9	18.8	15.8
Chronic heart failure	56.2	56.7	53.4	54.2	56.1	56.6	53.3	53.6
Cardiomyopathy	7.9	8.3	7.7	8.7	7.4	7.1	8.2	7.8
Other cardiac dysrhythmias	18.8	19.0	17.8	16.4	19.2	19.4	18.2	18.0
Valvular heart disease	26.1	27.1	24.9	24.6	25.7	25.6	23.5	22.3
Stroke/TIA	16.9	17.2	16.0	17.3	16.8	16.1	15.9	15.0
Peripheral vascular disease	27.7	27.5	26.6	25.9	27.3	26.2	25.6	23.2
Dyslipidemia	54.4	53.3	54.2	55.8	53.9	54.0	55.5	53.8
Diabetes	45.1	46.1	46.4	49.9	43.1	42.7	47.3	46.9
Major bleeding	38.5	38.3	37.0	39.3	38.3	37.0	36.2	34.8
Major intracranial bleeding	3.7	3.7	3.5	5.7	3.9	3.5	4.2	3.8
Major gastrointestinal bleeding	8.3	9.5	7.9	7.7	8.7	8.1	7.9	7.9
Other sites of major bleeding	32.0	30.9	30.9	32.4	31.8	31.2	29.8	28.8
Liver disease	2.6	2.8	2.9	2.9	2.5	2.4	2.7	2.5
Chronic obstructive pulmonary disease/asthma	44.0	44.2	46.0	49.7	42.2	42.1	44.5	45.3
Depression	11.8	11.5	12.2	11.8	11.7	11.4	12.1	11.9
Medical procedures (three years prior to cohort entry)								
Cardiac catheterization	5.0	5.4	5.2	5.3	5.0	4.9	6.4	6.4
Percutaneous coronary intervention-stent	4.1	3.9	3.8	4.1	3.8	4.0	4.1	4.0
Coronary artery bypass grafting	0.6	0.5	0.8	0.7	0.5	0.5	1.2	1.2
Implantable cardiac device	0.1	0.1	< 0.1	< 0.1	< 0.1	0.0	< 0.1	0.0

Medications (two weeks prior to cohort entry)								
Statin	51.0	51.2	51.1	52.9	50.0	47.9	50.6	50.4
Antiplatelet	8.7	8.5	8.1	8.9	8.3	7.4	8.1	7.9
Low-dose ASA	35.3	35.5	34.8	35.2	35.6	34.9	33.9	33.4
Proton pump inhibitors	49.7	49.6	47.8	46.9	50.0	49.1	46.4	44.7
NSAIDs	0.9	0.9	1.3	1.6	0.9	1.0	1.2	1.2
Digoxin	9.3	10.6	9.1	10.1	9.2	9.0	8.9	8.7
Amiodarone	9.6	9.3	8.6	6.1	9.3	9.8	8.8	8.0
Antidepressants	10.5	10.1	10.4	10.5	10.6	10.3	10.2	10.4
Beta-blockers	62.5	63.1	61.4	61.1	63.8	62.8	62.4	62.5
Calcium channel blockers	42.9	42.6	41.9	39.8	42.7	43.2	41.4	41.0
Inhibitors of the renin-angiotensin system	37.5	36.9	38.1	38.5	38.0	36.5	38.0	38.3
Diuretics	60.5	60.3	61.4	61.0	61.0	60.8	60.3	60.4
Loop diuretics	56.2	55.8	57.0	54.4	56.4	56.7	55.4	56.3
Antidiabetics	27.4	28.0	28.7	30.3	26.5	25.8	29.2	29.3
Health medical services (one year prior to cohort entry)								
Consultations with specialist physicians	1.2 ± 2.4	1.2 ± 1.9	1.2 ± 2.5	1.2 ± 2.3	1.2 ± 2.4	1.2 ± 2.2	1.2 ± 2.6	1.2 ± 1.8
Consultations with family physicians	1.3 ± 3.3	1.3 ± 2.8	1.2 ± 3.1	1.2 ± 2.5	1.3 ± 3.4	1.4 ± 3.0	1.2 ± 3.2	1.2 ± 2.6
Emergency visits	3.4 ± 3.1	3.4 ± 2.9	3.4 ± 3.4	3.5 ± 3.0	3.4 ± 3.1	3.5 ± 2.9	3.4 ± 3.3	3.3 ± 2.8
Health hospital services (three years prior to cohort entry)								
All-cause hospital admission	2.5 ± 2.1	2.5 ± 2.0	2.5 ± 2.4	2.6 ± 2.2	2.4 ± 2.0	2.5 ± 1.9	2.5 ± 2.3	2.4 ± 2.0

ASA: Acetylsalicylic acid; CKD: Chronic kidney disease; IPTW: Inverse probability of treatment weighting; NSAIDs: Nonsteroidal anti-inflammatory drugs; OAC: Oral anticoagulant; TIA: Transient ischemic attack.

Table 2 Sensitivity analysis of negative controls after inverse probability of treatment weighting in an on-treatment analysis

	Incident rate of rivaroxaban 15 mg 100 PY (95%CI)	Incident rate of warfarin 100 PY (95%CI)	HR (95%CI)[1]	*P* value
Diabetes complications	1.1 (0.2-2.0)	1.1 (0.6-1.5)	1.02 (0.40-2.60)	0.96
	Incident rate of rivaroxaban 20 mg 100 PY (95%CI)	Incident rate of warfarin 100 PY (95%CI)	HR (95%CI)[1]	*P* value
Diabetes complications	1.5 (0.6-2.4)	1.0 (0.6-1.5)	1.48 (0.72-3.06)	0.29
	Incident rate of apixaban 2.5 mg 100 PY (95%CI)	Incident rate of warfarin 100 PY (95%CI)	HR (95%CI)[1]	*P* value
Diabetes complications	0.8 (0.3-1.3)	1.2 (0.8-1.7)	0.66 (0.31-1.41)	0.28
	Incident rate of apixaban 5.0 mg 100 PY (95%CI)	Incident rate of warfarin 100 PY (95%CI)	HR (95%CI)	*P* value
Diabetes complications	0.7 (0.2-1.1)	1.4 (0.9-1.9)	0.49 (0.24-1.02)	0.06

A significant value is for $P < 0.05$ *vs* warfarin.

[1]For the negative control, we assessed the risk of diabetic complications (ICD-9: 250.1-250.9, 357.2, and 366.41; ICD-10: E10-E14 excluding E10.9, E11.9, E12.9, E13.0, and E14.9).

CI: Confidence interval; HR: Hazard ratio; PY: Person-years.

Table 3 E-values for significant comparisons in an on-treatment analysis after inverse probability of treatment weighting of new oral anticoagulant users with stage III chronic kidney disease

	Hazard ratio (95%CI)	E value corresponding to the CI bound closest to 1	E value for hazard ratio point estimate[1]
Apixaban 2.5 mg *vs* warfarin			
Safety composite	0.65 (0.43-0.99)	1.11	2.45
Apixaban 5.0 mg *vs* warfarin			
Effectiveness composite	0.76 (0.65-0.88)	1.53	1.96
All-cause mortality	0.61 (0.43-0.88)	1.53	2.66

[1]E-value for hazard used the point estimate instead of the bound closest to 1.
CI: Confidence interval.

confounding effects in our primary analysis and we provided several sensitivity analyses.

Our study also had some limitations. First, observational studies of administrative data are subject to confounding bias by unadjusted factors, such as the severity of AF, the exact eGFR, the international normalized ratio, body weight, over-the-counter prescriptions, and ethnicity. Second, use of administrative claims depends on comprehensive, accurate coding and recording of all diagnoses, drugs, and procedures. Third, it might not be possible to generalize our results to younger patients, or patients treated with other DOACs (dabigatran and edoxaban). Fourth, the effect sizes for individual safety and effectiveness outcomes were small. Fifth, we could not use time spent in the therapeutic range to assess the appropriateness of warfarin dosing, since our database did not record the international normalized ratio. Finally, our study did not include exact eGFR values; however, we estimated eGFR using an algorithm known to be valid in older adults[31].

CONCLUSION

In this observational study of new OAC users with AF and stage III CKD, we found that rivaroxaban is safe and effective relative to warfarin but if CrCl is between 30-49 mL/min, we need to reduce the dose to 15 mg. Apixaban 2.5 mg might even have a better safety profile than warfarin, while apixaban 5.0 mg might have a better effectiveness profile than warfarin, including a reduction in deaths. Appropriately sized RCTs are needed to confirm these findings in stage III CKD patients.

ARTICLE HIGHLIGHTS

Research background

The effectiveness and safety of apixaban and rivaroxaban in patients with atrial fibrillation (AF) and stage III chronic kidney disease (CKD) are not well established.

Research motivation

Few studies have evaluated the safety and efficacy of individual direct oral anticoagulants *vs* warfarin, nor have they established how dose selection impacts patients with AF and stage III CKD with respect to the incidence of stroke/systemic embolism (SE), major bleeding, and death.

Research objectives

We assessed and compared the effectiveness and safety of standard-dose rivaroxaban, low-dose rivaroxaban, standard-dose apixaban, and low-dose apixaban *vs* warfarin in a representative group of patients with AF and stage III CKD.

Research methods

A cohort of new users of apixaban, rivaroxaban or warfarin in AF patients and stage III CKD was created using administrative databases. We defined the effectiveness as a composite of stroke, SE or death; safety was defined as a composite of major bleeding within 1-year of follow-up. Comparisons were under treatment analysis using inverse probability of treatment weighting and Cox models.

Research results

Rivaroxaban 15 mg and 20 mg were associated with a similar efficacy and safety composite risk *vs* warfarin. Apixaban 5.0 mg was linked with decreased effectiveness composite risk [hazard ratio (HR) 0.76; 0.65-0.88] and a similar safety risk

(HR 0.94; 0.66-1.35), compared with apixaban 2.5 mg, which was associated with a similar effectiveness composite (HR 1.00; 0.79-1.26) and a lower safety risk (HR 0.65; 0.43-0.99).

Research conclusions

This observational study of new users of rivaroxaban and apixaban find that both appear to be safe and effective compared to warfarin in patients with AF and stage III CKD. Apixaban 2.5 mg might even have a better safety profile than warfarin, while apixaban 5.0 mg might have a better effectiveness profile than warfarin, to a reduction in deaths.

Research perspectives

The research perspective should be an appropriately sized randomized controlled trials to confirm these findings in AF patients with stage III CKD.

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FOOTNOTES

Author contributions: Perreault S, Boivin-Proulx LA, Lenglet A and Massy ZA contributed equally to concept, writing, and revising of the manuscript; Dorais M contributed to data analysis, figures, and reviewed the manuscript.

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REFERENCES

1 **Ananthapanyasut W**, Napan S, Rudolph EH, Harindhanavudhi T, Ayash H, Guglielmi KE, Lerma EV. Prevalence of atrial fibrillation and its predictors in nondialysis patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2010; **5**: 173-181 [PMID: 20007681 DOI: 10.2215/CJN.03170509]

2 **Soliman EZ**, Prineas RJ, Go AS, Xie D, Lash JP, Rahman M, Ojo A, Teal VL, Jensvold NG, Robinson NL, Dries DL, Bazzano L, Mohler ER, Wright JT, Feldman HI; Chronic Renal Insufficiency Cohort (CRIC) Study Group. Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC). *Am Heart J* 2010; **159**: 1102-1107 [PMID: 20569726 DOI: 10.1016/j.ahj.2010.03.027]

3 **Baber U**, Howard VJ, Halperin JL, Soliman EZ, Zhang X, McClellan W, Warnock DG, Muntner P. Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Circ Arrhythm Electrophysiol* 2011; **4**: 26-32 [PMID: 21076159 DOI: 10.1161/CIRCEP.110.957100]

4 **Mitsuma W**, Matsubara T, Hatada K, Imai S, Saito N, Shimada H, Miyazaki S. Clinical characteristics of hemodialysis patients with atrial fibrillation: The RAKUEN (Registry of atrial fibrillation in chronic kidney disease under hemodialysis from Niigata) study. *J Cardiol* 2016; **68**:

148-155 [PMID: 26527113 DOI: 10.1016/j.jjcc.2015.08.023]

5 **Bonde AN**, Lip GY, Kamper AL, Fosbøl EL, Staerk L, Carlson N, Torp-Pedersen C, Gislason G, Olesen JB. Renal Function and the Risk of Stroke and Bleeding in Patients With Atrial Fibrillation: An Observational Cohort Study. *Stroke* 2016; **47**: 2707-2713 [PMID: 27758943 DOI: 10.1161/strokeaha.116.014422]

6 **Providência R**, Marijon E, Boveda S, Barra S, Narayanan K, Le Heuzey JY, Gersh BJ, Gonçalves L. Meta-analysis of the influence of chronic kidney disease on the risk of thromboembolism among patients with nonvalvular atrial fibrillation. *Am J Cardiol* 2014; **114**: 646-653 [PMID: 25001152 DOI: 10.1016/j.amjcard.2014.05.048]

7 **Andrade JG**, Aguilar M, Atzema C, Bell A, Cairns JA, Cheung CC, Cox JL, Dorian P, Gladstone DJ, Healey JS, Khairy P, Leblanc K, McMurtry MS, Mitchell LB, Nair GM, Nattel S, Parkash R, Pilote L, Sandhu RK, Sarrazin JF, Sharma M, Skanes AC, Talajic M, Tsang TSM, Verma A, Verma S, Whitlock R, Wyse DG, Macle L; Members of the Secondary Panel. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. *Can J Cardiol* 2020; **36**: 1847-1948 [PMID: 33191198 DOI: 10.1016/j.cjca.2020.09.001]

8 **Marzec LN**, Wang J, Shah ND, Chan PS, Ting HH, Gosch KL, Hsu JC, Maddox TM. Influence of Direct Oral Anticoagulants on Rates of Oral Anticoagulation for Atrial Fibrillation. *J Am Coll Cardiol* 2017; **69**: 2475-2484 [PMID: 28521884 DOI: 10.1016/j.jacc.2017.03.540]

9 **Haas S**, Camm AJ, Bassand JP, Angchaisuksiri P, Cools F, Corbalan R, Gibbs H, Jacobson B, Koretsune Y, Mantovani LG, Misselwitz F, Panchenko E, Ragy HI, Stepinska J, Turpie AG, Sawhney JP, Steffel J, Lim TW, Pieper KS, Virdone S, Verheugt FW, Kakkar AK; GARFIELD-AF Investigators. Predictors of NOAC versus VKA use for stroke prevention in patients with newly diagnosed atrial fibrillation: Results from GARFIELD-AF. *Am Heart J* 2019; **213**: 35-46 [PMID: 31128503 DOI: 10.1016/j.ahj.2019.03.013]

10 **Bohula EA**, Giugliano RP, Ruff CT, Kuder JF, Murphy SA, Antman EM, Braunwald E. Impact of Renal Function on Outcomes With Edoxaban in the ENGAGE AF-TIMI 48 Trial. *Circulation* 2016; **134**: 24-36 [PMID: 27358434 DOI: 10.1161/CIRCULATIONAHA.116.022361]

11 **Fox KA**, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, Paolini JF, Hankey GJ, Mahaffey KW, Patel MR, Singer DE, Califf RM. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J* 2011; **32**: 2387-2394 [PMID: 21873708 DOI: 10.1093/eurheartj/ehr342]

12 **Hijazi Z**, Hohnloser SH, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, Ezekowitz MD, Reilly PA, Siegbahn A, Yusuf S, Wallentin L. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. *Circulation* 2014; **129**: 961-970 [PMID: 24323795 DOI: 10.1161/CIRCULATIONAHA.113.003628]

13 **Hohnloser SH**, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, Keltai M, Lanas F, Lopes RD, Lopez-Sendon J, Granger CB, Wallentin L. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J* 2012; **33**: 2821-2830 [PMID: 22933567 DOI: 10.1093/eurheartj/ehs274]

14 **Chen HY**, Ou SH, Huang CW, Lee PT, Chou KJ, Lin PC, Su YC. Efficacy and Safety of Direct Oral Anticoagulants vs Warfarin in Patients with Chronic Kidney Disease and Dialysis Patients: A Systematic Review and Meta-Analysis. *Clin Drug Investig* 2021; **41**: 341-351 [PMID: 33709339 DOI: 10.1007/s40261-021-01016-7]

15 **Di Lullo L**, Tripepi G, Ronco C, De Pascalis A, Barbera V, Granata A, Russo D, Di Iorio BR, Paoletti E, Ravera M, Fusaro M, Bellasi A. Safety and effectiveness of rivaroxaban and warfarin in moderate-to-advanced CKD: real world data. *J Nephrol* 2018; **31**: 751-756 [PMID: 29882198 DOI: 10.1007/s40620-018-0501-7]

16 **Siontis KC**, Zhang X, Eckard A, Bhave N, Schaubel DE, He K, Tilea A, Stack AG, Balkrishnan R, Yao X, Noseworthy PA, Shah ND, Saran R, Nallamothu BK. Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States. *Circulation* 2018; **138**: 1519-1529 [PMID: 29954737 DOI: 10.1161/CIRCULATIONAHA.118.035418]

17 **Makani A**, Saba S, Jain SK, Bhonsale A, Sharbaugh MS, Thoma F, Wang Y, Marroquin OC, Lee JS, Estes NAM, Mulukutla SR. Safety and Efficacy of Direct Oral Anticoagulants Versus Warfarin in Patients With Chronic Kidney Disease and Atrial Fibrillation. *Am J Cardiol* 2020; **125**: 210-214 [PMID: 31780073 DOI: 10.1016/j.amjcard.2019.10.033]

18 **Schafer JH**, Casey AL, Dupre KA, Staubes BA. Safety and Efficacy of Apixaban Versus Warfarin in Patients With Advanced Chronic Kidney Disease. *Ann Pharmacother* 2018; **52**: 1078-1084 [PMID: 29871510 DOI: 10.1177/1060028018781853]

19 **Coleman CI**, Kreutz R, Sood NA, Bunz TJ, Eriksson D, Meinecke AK, Baker WL. Rivaroxaban Versus Warfarin in Patients With Nonvalvular Atrial Fibrillation and Severe Kidney Disease or Undergoing Hemodialysis. *Am J Med* 2019; **132**: 1078-1083 [PMID: 31054829 DOI: 10.1016/j.amjmed.2019.04.013]

20 **Loo SY**, Coulombe J, Dell'Aniello S, Brophy JM, Suissa S, Renoux C. Comparative effectiveness of novel oral anticoagulants in UK patients with non-valvular atrial fibrillation and chronic kidney disease: a matched cohort study. *BMJ Open* 2018; **8**: e019638 [PMID: 29371284 DOI: 10.1136/bmjopen-2017-019638]

21 **Shin JI**, Secora A, Alexander GC, Inker LA, Coresh J, Chang AR, Grams ME. Risks and Benefits of Direct Oral Anticoagulants across the Spectrum of GFR among Incident and Prevalent Patients with Atrial Fibrillation. *Clin J Am Soc Nephrol* 2018; **13**: 1144-1152 [PMID: 30002224 DOI: 10.2215/CJN.13811217]

22 **Liabeuf S**, Laville SM, Bieber B, Tu C, Stengel B, Wong MMY, Calice da Silva V, Fliser D, Robinson BM, Pecoits-Filho R, Massy ZA. Prescription of Direct Oral Anticoagulants to Patients With Moderate-to-Advanced CKD: Too Little or Just Right? *Kidney Int Rep* 2021; **6**: 2496-2500 [PMID: 34514213 DOI: 10.1016/j.ekir.2021.06.004]

23 **Wetmore JB**, Roetker NS, Yan H, Reyes JL, Herzog CA. Direct-Acting Oral Anticoagulants Versus Warfarin in Medicare Patients With Chronic Kidney Disease and Atrial Fibrillation. *Stroke* 2020; **51**: 2364-2373 [PMID: 32640949 DOI: 10.1161/STROKEAHA.120.028934]

24 **von Elm E**, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg* 2014; **12**: 1495-1499 [PMID: 25046131 DOI: 10.1016/j.ijsu.2014.07.013]

25 **Tamblyn R**, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Québec. *J Clin Epidemiol* 1995; **48**: 999-1009 [PMID: 7775999 DOI: 10.1016/0895-4356(94)00234-h]

26 **Eguale T**, Winslade N, Hanley JA, Buckeridge DL, Tamblyn R. Enhancing pharmacosurveillance with systematic collection of treatment indication in electronic prescribing: a validation study in Canada. *Drug Saf* 2010; **33**: 559-567 [PMID: 20553057 DOI: 10.2165/11534580-000000000-00000]

27 **Wilchesky M**, Tamblyn RM, Huang A. Validation of diagnostic codes within medical services claims. *J Clin Epidemiol* 2004; **57**: 131-141

[PMID: 15125622 DOI: 10.1016/S0895-4356(03)00246-4]

28 **Tamblyn R**, Reid T, Mayo N, McLeod P, Churchill-Smith M. Using medical services claims to assess injuries in the elderly: sensitivity of diagnostic and procedure codes for injury ascertainment. *J Clin Epidemiol* 2000; **53**: 183-194 [PMID: 10729691 DOI: 10.1016/s0895-4356(99)00136-5]

29 **Humphries KH**, Jackevicius C, Gong Y, Svensen L, Cox J, Tu JV, Laupacis A; Canadian Cardiovascular Outcomes Research Team. Population rates of hospitalization for atrial fibrillation/flutter in Canada. *Can J Cardiol* 2004; **20**: 869-876 [PMID: 15266356]

30 **Perreault S**, Shahabi P, Côté R, Dumas S, Rouleau-Mailloux É, Feroz Zada Y, Provost S, Mongrain I, Dorais M, Huynh T, Kouz S, Diaz A, Blostein M, de Denus S, Turgeon J, Ginsberg J, Lelorier J, Lalonde L, Busque L, Kassis J, Talajic M, Tardif JC, Dubé MP. Rationale, design, and preliminary results of the Quebec Warfarin Cohort Study. *Clin Cardiol* 2018; **41**: 576-585 [PMID: 29542828 DOI: 10.1002/clc.22948]

31 **Roy L**, Zappitelli M, White-Guay B, Lafrance JP, Dorais M, Perreault S. Agreement Between Administrative Database and Medical Chart Review for the Prediction of Chronic Kidney Disease G category. *Can J Kidney Health Dis* 2020; **7**: 2054358120959908 [PMID: 33101698 DOI: 10.1177/2054358120959908]

32 **Lambert L**, Blais C, Hamel D, Brown K, Rinfret S, Cartier R, Giguère M, Carroll C, Beauchamp C, Bogaty P. Evaluation of care and surveillance of cardiovascular disease: can we trust medico-administrative hospital data? *Can J Cardiol* 2012; **28**: 162-168 [PMID: 22230034 DOI: 10.1016/j.cjca.2011.10.005]

33 **Levy AR**, Tamblyn RM, Fitchett D, McLeod PJ, Hanley JA. Coding accuracy of hospital discharge data for elderly survivors of myocardial infarction. *Can J Cardiol* 1999; **15**: 1277-1282 [PMID: 10579743]

34 **Andrade JG**, Verma A, Mitchell LB, Parkash R, Leblanc K, Atzema C, Healey JS, Bell A, Cairns J, Connolly S, Cox J, Dorian P, Gladstone D, McMurtry MS, Nair GM, Pilote L, Sarrazin JF, Sharma M, Skanes A, Talajic M, Tsang T, Verma S, Wyse DG, Nattel S, Macle L; CCS Atrial Fibrillation Guidelines Committee. 2018 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. *Can J Cardiol* 2018; **34**: 1371-1392 [PMID: 30404743 DOI: 10.1016/j.cjca.2018.08.026]

35 **Deyo RA**, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; **45**: 613-619 [PMID: 1607900 DOI: 10.1016/0895-4356(92)90133-8]

36 **D'Hoore W**, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson comorbidity index with administrative data bases. *J Clin Epidemiol* 1996; **49**: 1429-1433 [PMID: 8991959 DOI: 10.1016/s0895-4356(96)00271-5]

37 **Crane SJ**, Tung EE, Hanson GJ, Cha S, Chaudhry R, Takahashi PY. Use of an electronic administrative database to identify older community dwelling adults at high-risk for hospitalization or emergency department visits: the elders risk assessment index. *BMC Health Serv Res* 2010; **10**: 338 [PMID: 21144042 DOI: 10.1186/1472-6963-10-338]

38 **Fillion V**, Sirois MJ, Gamache P, Guertin JR, Morin SN, Jean S. Frailty and health services use among Quebec seniors with non-hip fractures: a population-based study using adminsitrative databases. *BMC Health Serv Res* 2019; **19**: 70 [PMID: 30683094 DOI: 10.1186/s12913-019-3865-z]

39 **Austin PC**, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015; **34**: 3661-3679 [PMID: 26238958 DOI: 10.1002/sim.6607]

40 **Allan V**, Ramagopalan SV, Mardekian J, Jenkins A, Li X, Pan X, Luo X. Propensity score matching and inverse probability of treatment weighting to address confounding by indication in comparative effectiveness research of oral anticoagulants. *J Comp Eff Res* 2020; **9**: 603-614 [PMID: 32186922 DOI: 10.2217/cer-2020-0013]

41 **VanderWeele TJ**, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med* 2017; **167**: 268-274 [PMID: 28693043 DOI: 10.7326/M16-2607]

42 **Hindricks G**, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021; **42**: 373-498 [PMID: 32860505 DOI: 10.1093/eurheartj/ehaa612]

43 **Fu CM**, Li LC, Lee YT, Wang SW, Hsu CN. Apixaban vs. Warfarin in Atrial Fibrillation Patients With Chronic Kidney Disease. *Front Cardiovasc Med* 2021; **8**: 752468 [PMID: 34733897 DOI: 10.3389/fcvm.2021.752468]

44 **Patel MR**, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**: 883-891 [PMID: 21830957 DOI: 10.1056/NEJMoa1009638]

45 **Yao X**, Tangri N, Gersh BJ, Sangaralingham LR, Shah ND, Nath KA, Noseworthy PA. Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation. *J Am Coll Cardiol* 2017; **70**: 2621-2632 [PMID: 29169468 DOI: 10.1016/j.jacc.2017.09.1087]

46 **Koos R**, Mahnken AH, Mühlenbruch G, Brandenburg V, Pflueger B, Wildberger JE, Kühl HP. Relation of oral anticoagulation to cardiac valvular and coronary calcium assessed by multislice spiral computed tomography. *Am J Cardiol* 2005; **96**: 747-749 [PMID: 16169351 DOI: 10.1016/j.amjcard.2005.05.014]

47 **Shea MK**, O'Donnell CJ, Hoffmann U, Dallal GE, Dawson-Hughes B, Ordovas JM, Price PA, Williamson MK, Booth SL. Vitamin K supplementation and progression of coronary artery calcium in older men and women. *Am J Clin Nutr* 2009; **89**: 1799-1807 [PMID: 19386744 DOI: 10.3945/ajcn.2008.27338]

48 **Schurgers LJ**, Aebert H, Vermeer C, Bültmann B, Janzen J. Oral anticoagulant treatment: friend or foe in cardiovascular disease? *Blood* 2004; **104**: 3231-3232 [PMID: 15265793 DOI: 10.1182/blood-2004-04-1277]

49 **Elango K**, Javaid A, Khetarpal BK, Ramalingam S, Kolandaivel KP, Gunasekaran K, Ahsan C. The Effects of Warfarin and Direct Oral Anticoagulants on Systemic Vascular Calcification: A Review. *Cells* 2021; **10** [PMID: 33807457 DOI: 10.3390/cells10040773]

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Retrospective Cohort Study

Bleeding complications after percutaneous kidney biopsies – nationwide experience from Brunei Darussalam

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Abstract

BACKGROUND

Kidney biopsy serves as a valuable method for both diagnosing and monitoring kidney conditions. Various studies have identified several risk factors associated with bleeding complications following the procedure, but these findings have shown inconsistency and variation.

AIM

To investigate the risk of bleeding complications following percutaneous kidney biopsy in Brunei Darussalam. We sought to explore the relevant clinical and pathological risk factors associated with these complications while also considering the findings within the broader international literature context.

METHODS

We conducted a retrospective study of all adult patients who underwent kidney biopsy in Brunei Darussalam from October 2013 to September 2020. The outcomes of interest were post-biopsy bleeding and the need for blood transfusions. Demographics, clinical, laboratory and procedural-related data were collected. Logistic regression analysis was used to identify predictors of outcomes.

RESULTS

A total of 255 kidney biopsies were included, with 11% being performed on transplanted kidneys. The majority of biopsies were done under ultrasound guidance (83.1%), with the rest under computer tomography guidance (16.9%). The most common indications for biopsy were chronic kidney disease of undefined cause (36.1%), nephrotic syndrome (24.3%) and acute kidney injury (11%). Rate of bleeding complication was 6.3% – 2% frank hematuria and 4.3% perinephric hematoma. Blood transfusion was required in 2.8% of patients. No patient lost a kidney or died because of the biopsy. Multivariate logistic regression identified baseline hemoglobin [odds ratio (OR): 4.11; 95% confidence interval (95%CI): 1.12-15.1; P = 0.03 for hemoglobin ≤ 11 g/dL *vs.* > 11 g/dL) and the

presence of microscopic hematuria (OR: 5.24; 95%CI: 1.43-19.1; P = 0.01) as independent risk factors for post-biopsy bleeding. Furthermore, low baseline platelet count was identified as the dominant risk factor for requiring post-biopsy transfusions. Specifically, each 10 10^9/L decrease in baseline platelet count was associated with an 12% increase risk of needing transfusion (OR: 0.88; 95%CI: 0.79-0.98; P = 0.02).

CONCLUSION
Kidney biopsies were generally well-tolerated. The identified risk factors for bleeding and transfusion can help clinicians to better identify patients who may be at increased risk for these outcomes and to provide appropriate monitoring and management.

Key Words: Kidney biopsy; Bleeding complications; Logistic regression; Retrospective cohort study; Risk

Core Tip: This retrospective study in Brunei Darussalam examined kidney biopsies from 2013 to 2020 and identified key risk factors for post-biopsy bleeding complications. Notably, it revealed that the presence of microscopic hematuria is a significant, previously unrecognized risk factor for such complications. Other findings included the impact of low baseline hemoglobin levels and platelet counts on bleeding and transfusion risk. These insights can assist clinicians in identifying high-risk patients and improving post-biopsy monitoring and care. Overall, the study enhances our understanding of kidney biopsy outcomes and patient safety.

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INTRODUCTION

A kidney biopsy is a procedure used to diagnose and monitor kidney disease. However, it is not without risks, with bleeding being a major complication due to its invasive nature. Bleeding complications can range from self-limited hematuria and asymptomatic perinephric hematomas, to life-threatening hemorrhage that can lead to serious consequences such as hemodynamic instability, kidney loss, and even death. In current practice, kidney biopsies are commonly performed percutaneously using real-time ultrasound guidance, which has been shown to decrease the risk of complications[1,2]. Moreover, automated spring-loaded biopsy devices have been found to be more effective than hand-driven systems, resulting in a higher yield of glomeruli and a reduction in major complications[3-5].

The frequency of complications following percutaneous native kidney biopsies varies across studies, mainly due to differences in patient populations, procedural techniques, complication definitions, and post-procedural monitoring. Although several risk factors for bleeding complications have been identified in different studies, the findings have been inconsistent[6]. A recent systematic review and meta-analysis that included 118064 biopsies reported that hematomas occurred in 11% of cases, frank hematuria in 3.5%, bleeding requiring blood transfusions in 1.6%, and interventions to stop bleeding in 0.3%[7].

In this study, we aimed to further investigate the risk of bleeding complications after percutaneous kidney biopsy and explore the associated clinical and pathologic risk factors. The study focused on a cohort of patients who underwent biopsies in Brunei Darussalam. By analyzing this specific group, the researchers aimed to provide more insights into the local context and shed light on factors that may contribute to bleeding complications.

MATERIALS AND METHODS

Study design and population

In this retrospective study, medical records of adult patients aged 18 years and above were reviewed over a period of seven years, from October 1, 2013, to September 30, 2020. The objective was to identify major bleeding complications associated with kidney biopsies. The analysis included only the first biopsy for patients who had multiple procedures. Kidney biopsy requests made by renal physicians were included, while those requested by urologists for investigating kidney lesions were excluded. Prior to the biopsy, informed consent was obtained from each patient. All antiplatelet and anticoagulation medications were stopped at least five days before the procedure, following the guidelines of the Society of Interventional Radiology[8]. Coagulation tests were performed a day before the biopsy, and if required, they were corrected using fresh frozen plasma or vitamin K to normalize the results. Pre-biopsy desmopressin was not administered. The biopsies were carried out in an inpatient setting, under local anesthesia, and with the guidance of

imaging techniques such as ultrasound or computed tomography (CT). In all cases, Bard Max-Core™ disposable core biopsy instrument with 18-gauge needles were used, typically performing 2 or 3 passes in the lower left renal pole, with the patient in the prone position. The decision on the number of passes was made by the procedurist based on whether sufficient core samples were obtained. After the procedure, patients were prescribed strict bed rest in a supine position for at least 6 h and monitored for post-procedure hematuria. Imaging was conducted immediately after the biopsy to confirm hemostasis, but further imaging to detect perinephric hematoma was only performed if clinically necessary. Perinephric hematoma was defined as the presence of hematoma on imaging that was over 1 cm in any dimension. Full blood counts were routinely performed the next day, and blood transfusions were given if clinically indicated. The decision to resume antiplatelet medications for patients at high cardiovascular risk was made on an individual basis, considering the risks and benefits. The study adhered to the ethical standards outlined in the Declaration of Helsinki and received approval from the institutional review board. A waiver of consent was granted by the Medical and Health Research and Ethics Committee.

Outcomes and covariates

Data on biopsy-associated bleeding events were collected by review of patient records. Outcomes of interest were post-biopsy bleeding (frank hematuria and/or perinephric hematoma), the need for blood transfusions, angiographic or open surgical interventions to control bleeding, nephrectomy and death. The timings of these bleeding events in relation to the procedure were also recorded.

Covariates examined included demographics (age, gender, ethnicity, height, weight), clinical (presence of hypertension, diabetes, whether dialysis was required before biopsy, biopsy indication), pre-biopsy laboratory (hemoglobin, platelet, serum creatinine, urea, albumin, total cholesterol, urine red blood cell, urine protein:creatinine ratio) and procedural-related (native or graft kidney, right or left kidney, procedurist, ultrasound or CT guided, number of passes, number of cores obtained) data.

Statistical analysis

mean ± SD were calculated for continuous parametric data, and medians and interquartile ranges for non-parametric data. Categorical data were reported using frequencies. For group comparisons, we used the Student *t*-test, Mann-Whitney test, chi-square test or Fisher exact test, as appropriate.

Logistic regression analysis was used to identify risk factors associated with the outcomes. Univariate analysis was done for each variable, using the Wald test. Any variable with a significant univariate test at P value < 0.1 was then selected as a candidate for the multivariate model along with all variables of known biologic importance. We chose this P value cut-off point as more traditional levels such as 0.05 can fail in identifying variables known to be important.

Following the fit of the multivariable model, iterative process of variable selection was done where covariates were removed from the model if they were non-significant and not a confounder. Significant was evaluated at the 0.05 alpha level and confounding as a change in any remaining parameter estimate greater than 15% as compared to the full model. At the end of this iterative process, the model contains significant covariates and confounders. Any variable not selected for the original multivariate model is added back one at a time, with significant covariates and confounders retained earlier. Any that are significant at the 0.05 level are put in the model, and the model is iteratively reduced as before but only for the variables that were additionally added.

All statistical analyses were performed using STATA software application version 17.

RESULTS

Over the 7-year period, 255 kidney biopsies were performed (Tables 1 and 2). The mean age of the patients were 35.5 years old, with mean weight of 72.3 kg. Out of the total, 28 procedures (11%) were conducted on transplanted kidneys. Notably, those performed with CT-guidance (16.9%) tended to involve patients with a higher average weight compared to those guided by ultrasound scan (83.1%) – with mean weights of 92 kg *vs.* 68 kg, respectively (P < 0.001). Forty-six percent of the patients had history of hypertension and 21% had history of diabetes. The primary reasons for performing biopsies were as follows: Chronic kidney disease of unspecified cause (36%), nephrotic syndrome (24%), and acute kidney injury (AKI) (11%). 10.2% of patients needed dialysis pre-biopsy. This decision was left at the discretion of the attending nephrologists. The median pre-biopsy serum creatinine was 158 [interquartile range (IQR): 80 to 381] μmol/L, hemoglobin 11.5 ± 2.6 g/dL and platelet count 300 ± 108.3 10^9/L. Out of the 255 kidney biopsies performed, only 5 patients exhibited minor abnormalities in their coagulation tests prior to the procedure. This 2% incidence was deemed statistically insignificant. Importantly, none of these 5 patients experienced any bleeding complications post-biopsy. Consequently, our team decided not to incorporate coagulation tests as predictive factors. Moreover, it is worth noting that the occurrence of post-biopsy bleeding could not be linked to abnormal coagulation test results, as all patients involved in this study displayed normal coagulation results or had their abnormalities corrected before the biopsy. The mean size of the biopsied kidney was 11 ± 1.4 cm. Majority (92.4%) needed two passes.

Bleeding complications were observed in 16 (6.3%) patients, with 4.3% developing a perinephric hematoma and 2% experiencing frank hematuria. These bleeding complications happened at a median of 1-hour (IQR: 1-15 h) post-biopsy. The maximum duration was a 48 h delay. Blood transfusion was needed in a total of 7 (2.8%) patients. As shown in Tables 3 and 4, both bleeding complications and need for blood transfusion were associated with very similar risk factors in the univariate analysis – the presence of microscopic hematuria, 4 needle passes (compared to 2 passes), lower baseline hemoglobin, platelet, complements, higher serum creatinine, urea, as well as anti-double stranded DNA and antinuclear

Table 1 Characteristics of study cohort (continuous variables)

Variables	*N* = 255	Missing
Mean age in years	35.5 ± 14.3	
Mean weight (kg)	72.3 ± 20.1	21
Mean hemoglobin (g/dL)	11.5 ± 2.6	1
Mean platelet (× 10^9/L)	300 ± 108.3	1
Median creatinine (μmol/L)	158 (80-381)	
Median urea (mmol/L)	9.4 (5.5-15.8)	
Mean albumin (g/L)	30.1 ± 9.1	
Median cholesterol (mmol/L)	5.6 (4.6-8.2)	13
Median urine protein: Creatinine ratio (mg/mmol)	598 (239-1119)	20
Median 24hr urine total protein (g/day)	4.2 (1.7-7.8)	103
Mean complement C3 (g/L)	1 ± 0.4	43
Mean complement C4 (g/L)	0.28 ± 0.14	44
Mean size of biopsied kidney (cm)	11 ± 1.4	40

Table 2 Characteristics of study cohort (categorical variables)

Variables	Classifications	*N* = 255	Missing
Male gender		120 (47%)	
Ethnicity	Malay	207 (81.2%)	
	Chinese	6 (2.4%)	
	Indian	1 (0.4%)	
	Other	41 (16%)	
Presence of hypertension		116 (45.5%)	
Presence of diabetes		53 (20.8%)	
Dialysis before biopsy		26 (10.2%)	
Clinical syndrome	Isolated hematuria	4 (1.6%)	
	Isolated non-nephrotic proteinuria	25 (9.8%)	
	Hemo-proteinuria	26 (10.2%)	
	Nephritic syndrome	2 (0.8%)	
	RPGN	1 (0.4%)	
	Nephrotic syndrome	62 (24.3%)	
	Nephritic-nephrotic syndrome	10 (3.9%)	
	AKI	28 (11%)	
	CKD of undefined cause	92 (36.1%)	
	Other	5 (2%)	
Presence of urine RBC		108 (43.9%)	9
Presence of ANA		69 (29.5%)	31
Presence of anti-dsDNA		28 (15.5%)	74
Presence of ENA		28 (15.6%)	76
Presence of ANCA		8 (4.2%)	63
Presence of HBV		6 (2.6%)	27

Presence of HCV		2 (0.9%)	34
Presence of HIV		2 (1%)	45
Transplanted (*vs*. native) kidney		28 (11%)	
If native, right (*vs*. left) kidney		3 (1.3%)	
Procedurist	Radiologist 1	82 (34%)	15
	Radiologist 2	28 (11.6%)	
	Radiologist 3	68 (28.2%)	
	Radiologist 4	13 (5.4%)	
	Radiologist 5	49 (20.3%)	
	Radiologist 6	1 (0.4%)	
CT (*vs*. USS) guidance		43 (16.9%)	
Number of passes	1	1 (0.5%)	57
	2	183 (92.4%)	
	3	11 (5.6%)	
	4	3 (1.5%)	
Number of cores	1	3 (1.5%)	48
	2	188 (90.8%)	
	3	12 (5.8%)	
	4	4 (1.9%)	

RPGN: Rapidly progressive glomerulonephritis; AKI: Acute kidney injury; CKD: Chronic kidney disease; RBC: Red blood cell; ANA: Antinuclear antibody; Anti-dsDNA: Anti-double stranded DNA; ENA: Extractable nuclear antigen antibodies; ANCA: Antineutrophil cytoplasmic antibodies; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human Immunodeficiency virus; CT: Computer tomography; USS: Ultrasound scan.

antibodies positivity.

Multivariable logistic regressions were performed to assess factors associated with an increased risk of bleeding complications and the need for blood transfusion after kidney biopsy. As indicated in Table 3, there is a significant association between pre-biopsy hemoglobin levels [with an odds ratio (OR) of 4.11; 95% confidence interval (95%CI): 1.12-15.1; P = 0.03 for hemoglobin 11 g/dL *vs*. >11 g/dL) and the presence of microscopic hematuria (with an OR of 5.24; 95%CI: 1.43–19.1; P = 0.01), both linked to the occurrence of post-biopsy bleeding.

After adjustment for other variables, it was solely the pre-biopsy platelet level that emerged as the primary factor influencing the need for post-biopsy blood transfusions. For every decrease of 10000/μL in the initial platelet count, there was a corresponding 12% rise in the likelihood of requiring a blood transfusion (with an OR of 0.88; 95%CI: 0.79-0.98; P = 0.02). There was no death, nephrectomy or angiographic or open surgical interventions needed to control bleeding. No differences in outcomes were found regarding the biopsy time period, first period from 2013 to 2016 years and second period from 2017 to 2020 (data not shown).

DISCUSSION

Our study has provided further evidence of the safety of kidney biopsy. We did not observe any nephrectomy or death after kidney biopsies performed in these 7 years. In a large meta-analysis, the rate of nephrectomy and death were 0.01% and 0.02% respectively[9].

The incidence of bleeding complications, specifically perinephric hematoma and frank hematuria, was found to be similar to that reported in other studies such as by Pombas *et al*[10] (5.44% hematoma, 2.57% frank hematuria) and Xu *et al*[11] (5.8% hematoma, 4.8% frank hematuria). However, two meta-analyses conducted by Poggio *et al*[7] and Corapi *et al*[9] have reported a higher incidence of hematoma at 11% and 11.6% respectively, while the incidence of frank hematuria was found to be comparable at 3.5% in both meta-analyses.

In our study, the 2.8% incidence of blood transfusion after kidney biopsy is consistent with the findings of other studies such as Shidham *et al*[12] (2.48%). However, our rate is lower compared to some population-based studies from other countries such as United States (26%)[13], Canada (9%)[14], France (5%)[15], Boston (4.3%)[16] and Australia (4%)[17]. Some of these population-based studies overestimated the risks of blood transfusion as not all of the events were attributable to kidney biopsies, particularly if the cohort had high co-morbidities such as anemia and heart failure. On the other hand, our rate of blood transfusion is higher than some other studies, such as Poggio *et al*[7] (1.6%), Pombas *et al*[10] (1.2%), Andrulli *et al*[18] (1.1%), Corapi *et al*[9] (0.9%), Tøndel *et al*[19] (0.9%) and Kawaguchi *et al*[20] (0.8%).

Table 3 Odds ratios for bleeding complications

Variables	Classifications	Univariate logistic regression			Multivariate logistic regression[1]		
		OR	95%CI	*P* value	OR	95%CI	*P* value
Age (yr)		1.02	0.99-1.06	0.254			
Gender	Female	Reference					
	Male	0.49	0.17-1.47	0.204			
Ethnicity	Malay	Reference					
	Chinese	2.55	0.28-23.2	0.407			
	Indian	NA	NA	NA			
	Other	NA	NA	NA			
Mean weight (kg)		1.01	0.98-1.04	0.428			
Hypertension	No	Reference					
	Yes	1.2	0.44-3.31	0.720			
Diabetes	No	Reference					
	Yes	1.8	0.60-5.42	0.297			
Dialysis before biopsy	No	Reference					
	Yes	2.16	0.57-8.13	0.256			
Clinical syndrome	AKI	Reference					
	Isolated hematuria	NA	NA	NA			
	Isolated non-nephrotic proteinuria	NA	NA	NA			
	Hemo-proteinuria	0.33	0.03-3.43	0.355			
	Nephritic syndrome	NA	NA	NA			
	RPGN	NA	NA	NA			
	Nephrotic syndrome	0.28	0.04-1.80	0.180			
	Nephritic-nephrotic syndrome	NA	NA	NA			
	CKD of undefined cause	1.02	0.26-3.98	0.982			
	Other	NA	NA	NA			
Mean hemoglobin (g/dL)	> 11	Reference			Reference		
	≤ 11	5.04	1.40-18.15	0.013[2]	4.11	1.12-15.1	0.033
Mean platelet (× 10^9/L)	> 250	Reference					
	≤ 250	3.23	1.13-9.20	0.028[2]			
Median creatinine (μmol/L)	< 265	Reference					
	≥ 265	3.62	1.27-10.3	0.016[2]			
Median urea (mmol/L)	< 10	Reference					
	≥ 10	3.8	1.19-12.12	0.024[2]			
Mean albumin (g/L)		0.95	0.90-1.01	0.080[2]			
Median cholesterol (mmol/L)		0.91	0.75-1.11	0.346			
Presence of urine RBC	No	Reference			Reference		
	Yes	6.1	1.7-22	0.006[2]	5.24	1.43-19.1	0.012
Median urine protein:creatinine ratio (mg/mmol)		1	0.9996-1.0005	0.787			

Median 24 h urine total protein (g/day)		0.92	0.78-1.09	0.351
Mean complement C3 (g/L)	≥ 0.8	Reference		
	< 0.8	3.35	1.20-9.36	0.021[2]
Mean complement C4 (g/L)	≥ 0.15	Reference		
	< 0.15	3.41	1.10-10.5	0.033[2]
Presence of ANA	No	Reference		
	Yes	2.98	1.03-8.58	0.044[2]
Presence of anti-dsDNA	No	Reference		
	Yes	3.94	1.19-13.1	0.025[2]
Presence of ENA	No	Reference		
	Yes	1.89	0.48-7.48	0.363
Presence of ANCA		NA	NA	NA
Presence of HBV		NA	NA	NA
Presence of HCV		NA	NA	NA
Presence of HIV		NA	NA	NA
Kidney type	Native	Reference		
	Transplanted	0.52	0.07-4.10	0.536
Site of kidney		NA	NA	NA
Mean size of biopsied kidney (cm)	> 12	Reference		
	≤ 12	2.11	0.58-7.63	0.254
Procedurist	Radiologist 1	Reference		
	Radiologist 2	0.30	0.04-2.48	0.265
	Radiologist 3	0.51	0.15-1.73	0.277
	Radiologist 4	0.68	0.08-5.83	0.722
	Radiologist 5	0.17	0.02-1.38	0.101
	Radiologist 6	NA	NA	NA
Guidance	Ultrasound	Reference		
	CT	2.39	0.79-7.28	0.124
Number of passes	1	NA	NA	NA
	2	Reference		
	3	NA	NA	NA
	4	8.65	0.72-103.7	0.089[2]
Number of cores	1	35.6	2.97-426.6	0.005[2]
	2	Reference		
	3	NA	NA	NA
	4	5.93	0.57-62.3	0.138

[1]Only *P* value < 0.05 in the multivariate analysis is shown.
[2]*P* value < 0.1.
OR: Odds ratio; 95%CI: 95% confidence interval; NA: Not applicable (as zero cell count); AKI: Acute kidney injury; RPGN: Rapidly progressive glomerulonephritis; CKD: Chronic kidney disease; RBC: Red blood cell; ANA: Antinuclear antibody; Anti-dsDNA: Anti-double stranded DNA; ENA: Extractable nuclear antigen antibodies; ANCA: Antineutrophil cytoplasmic antibodies; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human Immunodeficiency virus; CT: Computer tomography.

Table 4 Odds ratios for blood transfusion

Variables	Classifications	Univariate logistic regression			Multivariate logistic regression[1]		
		OR	95%CI	*P* value	OR	95%CI	*P* value
Age (yr)		1.00	0.95-1.05	0.951			
Gender	Female	Reference					
	Male	0.44	0.08-2.33	0.338			
Ethnicity	Malay	Reference					
	Chinese	NA	NA	NA			
	Indian	NA	NA	NA			
	Other	NA	NA	NA			
Mean weight (kg)		0.99	0.95-1.04	0.809			
Hypertension	No	Reference					
	Yes	0.89	0.19-4.06	0.880			
Diabetes	No	Reference					
	Yes	0.63	0.07-5.31	0.667			
Dialysis before biopsy	No	Reference					
	Yes	NA	NA	NA			
Clinical syndrome	AKI	Reference					
	Isolated hematuria	NA	NA	NA			
	Isolated non-nephrotic proteinuria	NA	NA	NA			
	Hemo-proteinuria	NA	NA	NA			
	Nephritic syndrome	NA	NA	NA			
	RPGN	NA	NA	NA			
	Nephrotic syndrome	0.45	0.03-7.47	0.577			
	Nephritic-nephrotic syndrome	NA	NA	NA			
	CKD of undefined cause	1.55	0.17-13.9	0.694			
	Other	NA	NA	NA			
Mean hemoglobin (g/dL)	> 11	Reference					
	≤ 11	6.67	0.79-56.2	0.081[2]			
Mean platelet (10×10^9/L)		0.88	0.79-0.98	0.021[2]	0.88	0.79-0.98	0.021
Median creatinine (μmol/L)		1.001	0.999-1.003	0.105			
Median urea (mmol/L)		1.068	0.999-1.141	0.052[2]			
Mean albumin (g/L)		0.93	0.86-1.01	0.105			
Median cholesterol (mmol/L)		0.94	0.71-1.24	0.654			
Presence of urine RBC	No	Reference					
	Yes	8	0.95-67.5	0.056[2]			
Median urine protein:creatinine ratio (mg/mmol)		1	0.9997-1.0006	0.415			
Median 24 h urine total protein (g/day)		0.88	0.66-1.18	0.389			
Mean complement C3 (g/L)	≥ 0.8	Reference					

	< 0.8	6.32	1.20-33.3	0.030[2]
Mean complement C4 (g/L)	≥ 0.15	Reference		
	< 0.15	5.43	1.16-25.4	0.032[2]
Presence of ANA	No	Reference		
	Yes	6.39	1.21-33.8	0.029[2]
Presence of anti-dsDNA	No	Reference		
	Yes	12.6	2.18-72.5	0.005[2]
Presence of ENA	No	Reference		
	Yes	2.83	0.49-16.2	0.244
Presence of ANCA		NA	NA	NA
Presence of HBV		NA	NA	NA
Presence of HCV		NA	NA	NA
Presence of HIV		NA	NA	NA
Kidney type	Native	Reference		
	Transplanted	1.36	0.16-11.7	0.781
Site of kidney		NA	NA	NA
Mean size of biopsied kidney (cm)	> 12	Reference		
	≤ 12	1.18	0.22-6.19	0.849
Procedurist	Radiologist 1	Reference		
	Radiologist 2	NA	NA	NA
	Radiologist 3	0.79	0.13-4.86	0.797
	Radiologist 4	2.17	0.21-22.6	0.518
	Radiologist 5	0.54	0.05-5.36	0.600
	Radiologist 6	NA	NA	NA
Guidance	Ultrasound	Reference		
	CT	0.81	0.10-6.93	0.850
Number of passes	1	NA	NA	NA
	2	Reference		
	3	NA	NA	NA
	4	22.4	1.67-300.3	0.019[2]
Number of cores	1	23	1.71-308.7	0.018[2]
	2	Reference		
	3	NA	NA	NA
	4	15.3	1.30-181.4	0.030[2]

[1]Only p-value < 0.05 in the multivariate analysis is shown.
[2]*p*-value < 0.1.
OR: Odds ratio; 95%CI: 95%confidence interval; NA: Not applicable (as zero cell count); AKI: Acute kidney injury; RPGN: Rapidly progressive glomerulonephritis; CKD: Chronic kidney disease; RBC: Red blood cell; ANA: Antinuclear antibody; Anti-dsDNA: Anti-double stranded DNA; ENA: Extractable nuclear antigen antibodies; ANCA: Antineutrophil cytoplasmic antibodies; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human Immunodeficiency virus; CT: Computer tomography.

Our study found that patients with low baseline hemoglobin were more likely to experience bleeding complications, while those with low baseline platelet counts had an increased risk of requiring blood transfusion. This is consistent with findings from other studies, such as Pombas *et al*[10] and Xu *et al*[11]. Specifically, we observed that with every decrease of 10000/μL in the initial platelet count, there was a corresponding 12% rise in the likelihood of necessitating a blood transfusion. This is comparable to the 11% increase reported in the Xu *et al*[11] study.

To our knowledge, our study is the first to show that the presence of microscopic hematuria is associated with bleeding complication following kidney biopsy. The reasons for this association are unclear, and it is possible that unmeasured confounding factors may contribute to both hematuria from glomerular bleeding and bleeding post-biopsy. Therefore, further evaluation in larger, prospective studies is needed before changes are made to clinical practice. Interestingly, a recent study by Andrulli *et al*[18] found that high proteinuria levels may actually protect against bleeding complications after biopsy. It is therefore important that variables including urinalysis (hematuria and/or proteinuria) be included in the regression models in future studies, to better elucidate this association.

Numerous studies have reported increased bleeding complications and the need for blood transfusions to be associated with factors such as presence of hypertension[12,21], presence of diabetes[22], poor kidney function[9,18,23,24], female [17,25,26], elderly[9,27], larger biopsy needle[9,28], higher number of needle passes[18], AKI as indication for biopsy[7,9,11,26]. We have not found these variables to be significant risk factors in our cohort. It is important to note that different studies may use different definitions of bleeding complications, have variation in patient selection, procedural technique or monitoring protocols, leading to variability in findings. Analyses of predictors of complications associated with kidney biopsy also vary across studies.

Our study found that majority of bleeding complications were identified within the first 1-15 h of the biopsy, but a significant proportion (2%-10%) occurred after 24 h[12,14,29]. Specifically, we observed that 6% of patients with bleeding complications experienced them after 24 h. Therefore, it is crucial to consider the appropriate post-biopsy observation period based on individual patient risk.

A strength of our study is the nationwide investigation that allowed for an extensive and in-depth analysis of risk factors for post-biopsy bleeding complications in the current era. However, our study has some limitations that should be considered. Our findings are limited by the relatively small sample size which may limit the power to detect significant associations. Residual confounding is also likely to be present in the retrospective study design. Additionally, we did not collect data on certain potential predictors, such as blood pressure and coagulation tests. We also did not evaluate the impact of antiplatelet use as it is already standard practice to withhold. Furthermore, a recent meta-analysis found no significantly increased risk for major bleeding complications in patients on aspirin[30]. Another limitation is that repeat imaging post-biopsy was not routinely performed, unless prompted by patient symptoms or hemodynamic instability. This may have led to ascertainment bias and potential underestimation of hematoma events.

Notwithstanding these limitations, the identified risk factors can still be utilized in clinical practice to effectively risk stratify patients and inform shared-decision making. Counseling patients on these known risks is imperative to achieving patient-centered care. We strongly suggest that modifiable risk factors be managed aggressively to lower the risk of bleeding.

CONCLUSION

In conclusion, our study shows that the risk of bleeding after kidney biopsy performed by radiologists is generally low. However, we found that bleeding complications were more frequent in patients with lower pre-biopsy hemoglobin level and those with microscopic hematuria. Patients with lower platelet counts also had a higher likelihood of requiring blood transfusion after kidney biopsy. While our findings support the safety of kidney biopsy, it is important to carefully evaluate patients in order to minimize the risks associated with the procedure.

ARTICLE HIGHLIGHTS

Research background

Kidney biopsy serves as a valuable method for both diagnosing and monitoring kidney conditions. However, various studies have identified several risk factors associated with bleeding complications following the procedure, but these findings have shown inconsistency and variation.

Research motivation

Identifying key factors that significantly predict complications following a kidney biopsy is valuable in providing patients with essential information when seeking their consent for the procedure.

Research objectives

Our primary objective was to investigate the risk of bleeding complications following percutaneous kidney biopsy in Brunei Darussalam. We sought to explore the relevant clinical and pathological risk factors associated with these complications while also considering the findings within the broader international literature context.

Research methods

We performed a retrospective review of records of patients who underwent percutaneous kidney biopsies in Brunei Darussalam from October 1, 2013 to September 30, 2020. The demographic, clinical, laboratory and procedural-related characteristics of the patients were reviewed.

Research results

A total of 255 kidney biopsies were included. The incidence of bleeding (including hematuria and perinephric hematoma) stood at 6.3%. Blood transfusions were deemed necessary for 2.8% of patients, and fortunately, no patient suffered kidney loss or mortality due to the biopsy procedure. In a multivariable logistic regression analysis, two factors emerged as independent risk contributors for post-biopsy bleeding: baseline hemoglobin levels and the presence of microscopic hematuria. Additionally, a lower baseline platelet count emerged as the primary risk factor associated with the need for post-biopsy transfusions.

Research conclusions

Our findings align with existing research regarding the predictive risk factors for post-kidney biopsy bleeding complications. Nevertheless, our study uniquely highlights that the presence of pre-biopsy microscopic hematuria represents a notable and previously unreported risk factor for these complications.

Research perspectives

While our findings support the safety of kidney biopsy, it is important to carefully evaluate patients in order to minimize the risks associated with the procedure.

FOOTNOTES

Author contributions: Lim CY designed the research, contributed to the statistical analysis, literature review, writing and revision; Khay SL collected the data and contributed to the writing and revision; all authors approved the paper.

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REFERENCES

1 **Burstein DM**, Schwartz MM, Korbet SM. Percutaneous renal biopsy with the use of real-time ultrasound. *Am J Nephrol* 1991; **11**: 195-200 [PMID: 1962666 DOI: 10.1159/000168303]
2 **Birnholz JC**, Kasinath BS, Corwin HL. An improved technique for ultrasound guided percutaneous renal biopsy. *Kidney Int* 1985; **27**: 80-82 [PMID: 3981874 DOI: 10.1038/ki.1985.13]
3 **Doyle AJ**, Gregory MC, Terreros DA. Percutaneous native renal biopsy: comparison of a 1.2-mm spring-driven system with a traditional 2-mm hand-driven system. *Am J Kidney Dis* 1994; **23**: 498-503 [PMID: 8154484 DOI: 10.1016/s0272-6386(12)80370-2]
4 **Riehl J**, Maigatter S, Kierdorf H, Schmitt H, Maurin N, Sieberth HG. Percutaneous renal biopsy: comparison of manual and automated puncture techniques with native and transplanted kidneys. *Nephrol Dial Transplant* 1994; **9**: 1568-1574 [PMID: 7870344]
5 **Burstein DM**, Korbet SM, Schwartz MM. The use of the automatic core biopsy system in percutaneous renal biopsies: a comparative study. *Am J Kidney Dis* 1993; **22**: 545-552 [PMID: 8213794 DOI: 10.1016/s0272-6386(12)80927-9]
6 **Whittier WL**. Complications of the percutaneous kidney biopsy. *Adv Chronic Kidney Dis* 2012; **19**: 179-187 [PMID: 22578678 DOI: 10.1053/j.ackd.2012.04.003]
7 **Poggio ED**, McClelland RL, Blank KN, Hansen S, Bansal S, Bomback AS, Canetta PA, Khairallah P, Kiryluk K, Lecker SH, McMahon GM, Palevsky PM, Parikh S, Rosas SE, Tuttle K, Vazquez MA, Vijayan A, Rovin BH; Kidney Precision Medicine Project. Systematic Review and Meta-Analysis of Native Kidney Biopsy Complications. *Clin J Am Soc Nephrol* 2020; **15**: 1595-1602 [PMID: 33060160 DOI:

10.2215/CJN.04710420]

8 **Patel IJ**, Davidson JC, Nikolic B, Salazar GM, Schwartzberg MS, Walker TG, Saad WA; Standards of Practice Committee, with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Endorsement. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. *J Vasc Interv Radiol* 2012; **23**: 727-736 [PMID: 22513394 DOI: 10.1016/j.jvir.2012.02.012]

9 **Corapi KM**, Chen JL, Balk EM, Gordon CE. Bleeding complications of native kidney biopsy: a systematic review and meta-analysis. *Am J Kidney Dis* 2012; **60**: 62-73 [PMID: 22537423 DOI: 10.1053/j.ajkd.2012.02.330]

10 **Pombas B**, Rodríguez E, Sánchez J, Radosevic A, Gimeno J, Busto M, Barrios C, Sans L, Pascual J, Soler MJ. Risk Factors Associated with Major Complications after Ultrasound-Guided Percutaneous Renal Biopsy of Native Kidneys. *Kidney Blood Press Res* 2020; **45**: 122-130 [PMID: 31822004 DOI: 10.1159/000504544]

11 **Xu J**, Wu X, Xu Y, Ren H, Wang W, Chen W, Shen P, Li X, Shi H, Xie J, Chen X, Zhang W, Pan X. Acute Kidney Disease Increases the Risk of Post-Kidney Biopsy Bleeding Complications. *Kidney Blood Press Res* 2020; **45**: 873-882 [PMID: 33105145 DOI: 10.1159/000509443]

12 **Shidham GB**, Siddiqi N, Beres JA, Logan B, Nagaraja HN, Shidham SG, Piering WF. Clinical risk factors associated with bleeding after native kidney biopsy. *Nephrology (Carlton)* 2005; **10**: 305-310 [PMID: 15958047 DOI: 10.1111/j.1440-1797.2005.00394.x]

13 **Al Turk AA**, Estiverne C, Agrawal PR, Michaud JM. Trends and outcomes of the use of percutaneous native kidney biopsy in the United States: 5-year data analysis of the Nationwide Inpatient Sample. *Clin Kidney J* 2018; **11**: 330-336 [PMID: 29988286 DOI: 10.1093/ckj/sfx102]

14 **Simard-Meilleur MC**, Troyanov S, Roy L, Dalaire E, Brachemi S. Risk factors and timing of native kidney biopsy complications. *Nephron Extra* 2014; **4**: 42-49 [PMID: 24803920 DOI: 10.1159/000360087]

15 **Halimi JM**, Gatault P, Longuet H, Barbet C, Bisson A, Sautenet B, Herbert J, Buchler M, Grammatico-Guillon L, Fauchier L. Major Bleeding and Risk of Death after Percutaneous Native Kidney Biopsies: A French Nationwide Cohort Study. *Clin J Am Soc Nephrol* 2020; **15**: 1587-1594 [PMID: 33060158 DOI: 10.2215/CJN.14721219]

16 **Palsson R**, Short SAP, Kibbelaar ZA, Amodu A, Stillman IE, Rennke HG, McMahon GM, Waikar SS. Bleeding Complications After Percutaneous Native Kidney Biopsy: Results From the Boston Kidney Biopsy Cohort. *Kidney Int Rep* 2020; **5**: 511-518 [PMID: 32274455 DOI: 10.1016/j.ekir.2020.01.012]

17 **Anpalahan A**, Malacova E, Hegerty K, Malett A, Ranganathan D, Healy HG, Gois PHF. Bleeding Complications of Percutaneous Kidney Biopsy: Does Gender Matter? *Kidney360* 2021; **2**: 1308-1312 [PMID: 35369661 DOI: 10.34067/KID.0002432021]

18 **Andrulli S**, Rossini M, Gigliotti G, La Manna G, Feriozzi S, Aucella F, Granata A, Moggia E, Santoro D, Manenti L, Infante B, Ferrantelli A, Cianci R, Giordano M, Giannese D, Seminara G, Di Luca M, Bonomini M, Spatola L, Bruno F, Baraldi O, Micarelli D, Piemontese M, Distefano G, Mattozzi F, De Giovanni P, Penna D, Garozzo M, Vernaglione L, Abaterusso C, Zanchelli F, Brugnano R, Gintoli E, Sottini L, Quaglia M, Cavoli GL, De Fabritiis M, Conte MM, Manes M, Battaglia Y, Fontana F, Gesualdo L; ITA-KID-BIO-Group. The risks associated with percutaneous native kidney biopsies: a prospective study. *Nephrol Dial Transplant* 2023; **38**: 655-663 [PMID: 35587882 DOI: 10.1093/ndt/gfac177]

19 **Tøndel C**, Vikse BE, Bostad L, Svarstad E. Safety and complications of percutaneous kidney biopsies in 715 children and 8573 adults in Norway 1988-2010. *Clin J Am Soc Nephrol* 2012; **7**: 1591-1597 [PMID: 22837269 DOI: 10.2215/CJN.02150212]

20 **Kawaguchi T**, Nagasawsa T, Tsuruya K, Miura K, Katsuno T, Morikawa T, Ishikawa E, Ogura M, Matsumura H, Kurayama R, Matsumoto S, Marui Y, Hara S, Maruyama S, Narita I, Okada H, Ubara Y; Committee of Practical Guide for Kidney Biopsy 2019. A nationwide survey on clinical practice patterns and bleeding complications of percutaneous native kidney biopsy in Japan. *Clin Exp Nephrol* 2020; **24**: 389-401 [PMID: 32189101 DOI: 10.1007/s10157-020-01869-w]

21 **Kriegshauser JS**, Patel MD, Young SW, Chen F, Eversman WG, Chang YH. Risk of bleeding after native renal biopsy as a function of preprocedural systolic and diastolic blood pressure. *J Vasc Interv Radiol* 2015; **26**: 206-212 [PMID: 25533452 DOI: 10.1016/j.jvir.2014.10.020]

22 **Hasegawa S**, Okada A, Aso S, Kumazawa R, Matsui H, Fushimi K, Yasunaga H, Nangaku M. Association Between Diabetes and Major Bleeding Complications of Renal Biopsy. *Kidney Int Rep* 2022; **7**: 232-240 [PMID: 35155862 DOI: 10.1016/j.ekir.2021.11.013]

23 **Korbet SM**, Volpini KC, Whittier WL. Percutaneous renal biopsy of native kidneys: a single-center experience of 1,055 biopsies. *Am J Nephrol* 2014; **39**: 153-162 [PMID: 24526094 DOI: 10.1159/000358334]

24 **Xu DM**, Chen M, Zhou FD, Zhao MH. Risk Factors for Severe Bleeding Complications in Percutaneous Renal Biopsy. *Am J Med Sci* 2017; **353**: 230-235 [PMID: 28262208 DOI: 10.1016/j.amjms.2016.12.019]

25 **Manno C**, Strippoli GF, Arnesano L, Bonifati C, Campobasso N, Gesualdo L, Schena FP. Predictors of bleeding complications in percutaneous ultrasound-guided renal biopsy. *Kidney Int* 2004; **66**: 1570-1577 [PMID: 15458453 DOI: 10.1111/j.1523-1755.2004.00922.x]

26 **Moledina DG**, Luciano RL, Kukova L, Chan L, Saha A, Nadkarni G, Alfano S, Wilson FP, Perazella MA, Parikh CR. Kidney Biopsy-Related Complications in Hospitalized Patients with Acute Kidney Disease. *Clin J Am Soc Nephrol* 2018; **13**: 1633-1640 [PMID: 30348813 DOI: 10.2215/CJN.04910418]

27 **Lees JS**, McQuarrie EP, Mordi N, Geddes CC, Fox JG, Mackinnon B. Risk factors for bleeding complications after nephrologist-performed native renal biopsy. *Clin Kidney J* 2017; **10**: 573-577 [PMID: 28852497 DOI: 10.1093/ckj/sfx012]

28 **Waldo B**, Korbet SM, Freimanis MG, Lewis EJ. The value of post-biopsy ultrasound in predicting complications after percutaneous renal biopsy of native kidneys. *Nephrol Dial Transplant* 2009; **24**: 2433-2439 [PMID: 19246472 DOI: 10.1093/ndt/gfp073]

29 **Prasad N**, Kumar S, Manjunath R, Bhadauria D, Kaul A, Sharma RK, Gupta A, Lal H, Jain M, Agrawal V. Real-time ultrasound-guided percutaneous renal biopsy with needle guide by nephrologists decreases post-biopsy complications. *Clin Kidney J* 2015; **8**: 151-156 [PMID: 25815170 DOI: 10.1093/ckj/sfv012]

30 **Relvas M**, Gonçalves J, Castro I, Diniz H, Mendonça L, Coentrão L. Effects of Aspirin on Kidney Biopsy Bleeding Complications: A Systematic Review and Meta-Analysis (PROSPERO 2021 CRD42021261005). *Kidney360* 2023; **4**: 700-710 [PMID: 36951435 DOI: 10.34067/KID.0000000000000091]

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ORIGINAL ARTICLE

Observational Study

The correlation of spot urinary protein-to-creatinine ratio with 24-h urinary protein excretion in various glomerulopathies

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Abstract

BACKGROUND

Proteinuria is an important and well-known biomarker of many forms of kidney injury. Its quantitation is of particular importance in the diagnosis and management of glomerular diseases. Its quantification can be done by several methods. Among these, the measurement of 24-h urinary protein excretion is the gold standard method. However, it is cumbersome, time-consuming, and inconvenient for patients and is not completely foolproof. Many alternative methods have been tested over time albeit with conflicting results. Among the latter, the measurement of urine protein-to-creatinine ratio (uPCR) in single-voided urinary samples is widely used. The majority of studies found a good correlation between uPCR in single urine samples with 24-h urinary protein estimation, whereas others did not.

AIM

To investigate the correlation of spot uPCR with 24-h urinary protein estimation in patients suffering from different forms of glomerulopathies at a single large-volume nephrological center in Pakistan.

METHODS

This cross-sectional, observational study was conducted at the Department of Nephrology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan from September 2017 to March 2018. All newly presenting adult patients with proteinuria who were being investigated for suspected glomerulonephritis and persistent proteinuria with ages between 18 to 60 years were enrolled. All patients were given detailed advice regarding 24-h urine collection starting at 7:00 AM for total protein and creatinine excretion estimations. A spot urine sample was collected the next day at the time of submission of a 24-h urine sample for

measuring uPCR along with a blood sample. The data of patients were collected in a proforma. SPSS version 20.0 was used for statistical analysis.

RESULTS

A total of 157 patients were included. Their mean age was 30.45 ± 12.11 years. There were 94 (59.8%) males and 63 (40.2%) females. The mean 24-h urinary protein excretion was 3192.78 ± 1959.79 mg and the mean spot uPCR was 3.16 ± 1.52 in all patients. A weak but significant correlation was observed between spot uPCR and 24-h urinary protein excretion (r = 0.342, P = 0.01) among all patients. On subgroup analysis, a slightly better correlation was found in patients older than 47 years (r = 0.78), and those with body mass index > 25 kg/m^2 (r = 0.45). The Bland and Altman's plot analysis comparing the differences between spot uPCR and 24-h protein measurement also showed a wide range of the limits of agreement between the two methods.

CONCLUSION

Overall, the results from this study showed a significant and weakly positive correlation between spot uPCR and 24-h urinary protein estimation in different forms of glomerulopathies. The agreement between the two methods was also poor. Hence, there is a need for careful interpretation of the ratio in an unselected group of patients with kidney disease.

Key Words: Glomerulopathies; 24-h proteinuria; Spot urinary protein-to-creatinine ratio; Correlation; Proteinuria; Agreement

Core Tip: The quantitation of proteinuria is of particular importance in the diagnosis and management of glomerulonephritides. The measurement of 24-h urinary protein excretion is the gold standard. However, it is cumbersome, time-consuming, and inconvenient for patients. The measurement of urine protein-to-creatinine ratio (uPCR) is the most popular alternative. Numerous studies have been conducted on the correlation of these two methods with conflicting results. We assessed the correlation and the degree of agreement between the two methods. We conclude that uPCR shows poor correlation and poor agreement with 24-h proteinuria. It must be interpreted with caution in an unselected group of glomerulopathies.

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INTRODUCTION

Proteinuria is an early sign of glomerular diseases and its quantification for the initial evaluation and follow-up of patients with glomerulonephritis (GN) is routine in clinical practice. It is not only indispensable in making a diagnosis but is also used in monitoring the treatment response of kidney diseases. In fact, remission of proteinuria in some glomerular diseases represents the most powerful predictive factor for ultimate clinical outcomes[1,2]. In some clinical settings, such as nephrotic syndrome, its magnitude directly reflects the disease activity. As protein excretion varies during the course of a day, its estimation in 24-h urine collection is the gold standard method for the evaluation of proteinuria, but this method is cumbersome, time-consuming, more expensive, uncomfortable to the patient, and prone to errors due to under-collection or over-collection of multiple voided samples in a time-dependent manner. Moreover, it cannot be performed in some groups of patients such as children, the elderly, and physically and mentally disabled patients[3-5]. Since 1983, when Ginsberg *et al*[6] used the ratio as an alternative to 24-h proteinuria, many studies have been carried out using protein-to-creatinine ratios (PCRs) in spot or single-voided urine samples in different clinical settings to correlate these results with 24-h proteinuria, with a correlation ranging from 0.6-0.9 in different studies[7-10]. However, urinary PCR (uPCR) is also influenced by certain features like age, sex, race, muscle mass, and the timing of the urine sample. A sole reliance on uPCR to start or defer specific immunosuppressive treatment without considering these features may be inappropriate. Low muscle mass in the South Asian population has been shown to be an important determinant of low creatinine excretion[11-17]. This is particularly true in elderly, females, and malnourished patients. All these conditions will cause a relatively high uPCR for the same degree of proteinuria.

The correlation between the above two methods of estimation of proteinuria is also influenced by types of renal disease, degree of deterioration in kidney function and degree of proteinuria. Weak correlation is observed in cases of severe kidney failure, interstitial nephritis or severe proteinuria[3-5].

There are very few studies from Pakistan comparing uPCR with 24-h urine protein excretion and only one was done in patients with normal glomerular filtration rate[13,14]. An excellent correlation (r = 0.96) was found between random uPCR and standard 24-h urinary protein excretion in these patients (P < 0.001)[13]. However, the difference between

uPCR and 24-h protein excretion was not reported.

The objective of this study was to compare estimated protein excretion by uPCR with measured 24-h urine protein excretion in patients with different types of glomerulopathies at a single center in Pakistan.

MATERIALS AND METHODS

This cross-sectional and observational study was conducted at the outpatient clinic of the Department of Nephrology, Sindh Institute of Urology and Transplantation between 28th September 2017 and 28th March 2018. Eligibility for the study were adult subjects with the suspected glomerular disease with dipstick-positive proteinuria on the day of recruitment. Consecutive patients who agreed to submit a 24-h urine sample, who were more than 18 years old, and who were not diabetic were included. Exclusion criteria were chronic kidney disease stage 5 based on the Cockcroft-Gault formula, urinary tract infection, and those deemed incapable of collecting 24-h urine.

All patients were informed about the study's purpose and written consent was obtained. Patients were given detailed advice regarding 24-h urine collection from morning to the next morning. A wide-mouthed container was provided to every patient for collecting the 24-h urine. Patients were asked to collect the 24-h urine of their most convenient day and bring it on the day of completion. A spot urine sample was taken on the submission day for measuring the uPCR. A blood sample was taken at the same time. All samples were transported to the laboratory immediately. Serum creatinine and urinary creatinine (mg/dL) concentrations were determined using the modified Jaffe's method on an auto-analyzer. Creatinine clearance was calculated by the standard formula. Urinary protein concentration was determined with the colorimetric method using pyrogallol red. To assess the completeness of the collection, creatinine excretion in a 24-h urine sample was used. Specimens with creatinine excretion of 15-25 mg/kg in males, and 12-20 mg/kg in females, were considered adequate. Patients with creatinine excretion outside these ranges were excluded from the study.

The statistical analysis for this research was done by using SPSS version 22.0 (IBM Corp, Armonk, NY, United States). mean ± SD were evaluated for continuous data such as age, weight, height, body mass index (BMI), 24-h urinary volume, urinary protein excretion, serum creatinine, creatinine clearance, and spot uPCR. For categorical data such as gender, the frequency and percentages were calculated. Correlation between spot uPCR and 24-h urinary protein excretion was carried out using Pearson's correlation coefficient (r). P-value ≤ 0.05 was taken as significant. Bland and Altman plot was drawn using the average of protein excretion by both the methods on the X-axis and the difference between 24-h urinary protein and spot uPCR on the Y-axis. Mean bias and 95% confidence limits for the degree of agreement between the two methods were also calculated.

RESULTS

The main demographic, clinical and laboratory characteristics of the study population (n = 157) are shown in Table 1. The mean age of all patients was 30.45 ± 12.11 years. There were 94 (59.8%) males and 63 (40.2%) females. The majority of the patients (n = 133, 74.53 %) had a BMI of < 25 kg/m^2. The mean values of urinary protein excretion by both methods were similar to each other, with maximum values of protein excretion by both being less than 10 g/24 h. The mean 24-h urinary creatinine excretion was 834.96 ± 391.43 mg/24 h. The histopathological results of kidney biopsies in these patients are also shown in Table 1. It is apparent that focal segmental glomerulosclerosis and membranous GN were the two most common lesions followed by a variety of less common other pathological lesions. A positive, fair, and significant correlation between spot uPCR and 24-h urinary protein excretion (r = 0.342, P-value < 0.001) in the entire group (Figure 1). On subgroup analysis, a slightly better correlation was found in patients older than 47 years, and those with BMI > 25 kg/m^2 (Table 2).

Bland and Altman's plot comparing the differences between spot uPCR and 24-h protein measurement is depicted in Figure 2. The mean bias was 373 mg; however, the limits of agreement were fairly wide (from -3682 to 4069 mg). The scatter of differences increased as the amount of proteinuria increased. The mean bias and limits of agreement in the groups with less than and more than 3000 mg protein excretion are shown in Figures 3 and 4, respectively. Briefly, the mean bias was -93.64 mg and the limits of agreement were -2861.53 to 2674.25 mg in the group of patients with less than 3000 mg of proteinuria. These values were 158.36 and -4738.46 to 5035.18 mg in the group of patients with more than 3000 mg of proteinuria. As is obvious, the limits are wider with increasing levels of proteinuria.

DISCUSSION

The quantification of proteinuria is an important investigation in patients with various glomerular diseases. It not only helps in making a diagnosis but also helps in follow-up to monitor disease progression, and often, important therapeutic decisions are made based on its exact value. The traditional reference method, 24-h urine protein measurement, is a cumbersome and tedious test, and therefore spot uPCR has replaced it in clinical practice due to its simplicity, convenience, and presumed accuracy. Initial studies focused more on the correlation between the two methods and not surprisingly a moderate to strong correlation (0.57 to 0.9) was reported in different studies[1-5].

In the present study, a fair correlation of spot uPCR with 24-h urinary protein measurement was observed. Although this was statistically significant, it is lower than the previously described correlation in many other studies[1-5,7-10,18-

Table 1 The main demographic, clinical, laboratory, and pathology characteristics of the study population (157)

Parameters	Values
Age (yr)	30.45 ± 12.108
Weight (kg)	59.70 ± 15.067
Height (cm)	163.98 ± 11.476
Body mass index (kg/m^2)	22.30 ± 5.65
Serum creatinine (mg/dL)	1.00 ± 0.54
24-h urinary creatinine (mg/24-h)	834.12 ± 391.43
Creatinine clearance (ml/min)	75.05 ± 33.55
Spot urine protein (mg/dL)	296.04 ± 159.65
Spot urine creatinine (mg/dL)	108.83 ± 58.01
24-h urine protein excretion (mg/24-h)	3192.78 ± 1959.79
Spot urine protein to creatinine ratio (mg/mg)	3.15 ± 1.52
24-h urine volume	1711.40 ± 882.03
Histopathological diagnosis, n (%)	
Focal segmental glomerulosclerosis	52 (33.12)
Membranous glomerulonephritis	44 (28)
Mesangiocapillary glomerulonephritis	28 (17.83)
IgM nephropathy	11 (7)
Lupus nephritis	10 (6.36)
Minimal change disease	4 (2.54)
Others	8 (5.09)

All values are in mean ± SD, unless otherwise specified.

Table 2 Correlation of spot urine protein-to-creatinine ratio with 24-h urinary protein estimation stratified according to age and body mass index

Parameters	No of patients (*n*)	Correlation coefficient (r)	*P* value
Age (yr) groups			
34-46	35	0.475	0.004
> 47	21	0.780	0.001
BMI (kg/m^2) ranges			
23-25	24	0.411	0.046
> 25	40	0.459	0.00
Proteinuria			
< 3000 mg/d	79	0.021	0.28
≥ 3000 mg/d	78	0.216	0.058

BMI: Body mass index.

21]. These results are not entirely explained on the basis of extremes of proteinuria in our population. The median protein excretion in our population was 2970 mg in 24 h, and we, therefore, stratified them according to proteinuria above and below 3000 mg to see if the correlation changes, as most of the therapeutic decisions are taken when proteinuria is above 3000 mg. There was an equal number of patients in the two groups (79 in < 3000 mg group, and 78 in ≥ 3000 mg group). The correlation was much weaker in the group with protein excretion of less than 3000 mg and failed to reach statistical significance. In the group with protein excretion of more than 3000 mg in 24 h, the correlation with spot uPCR was just

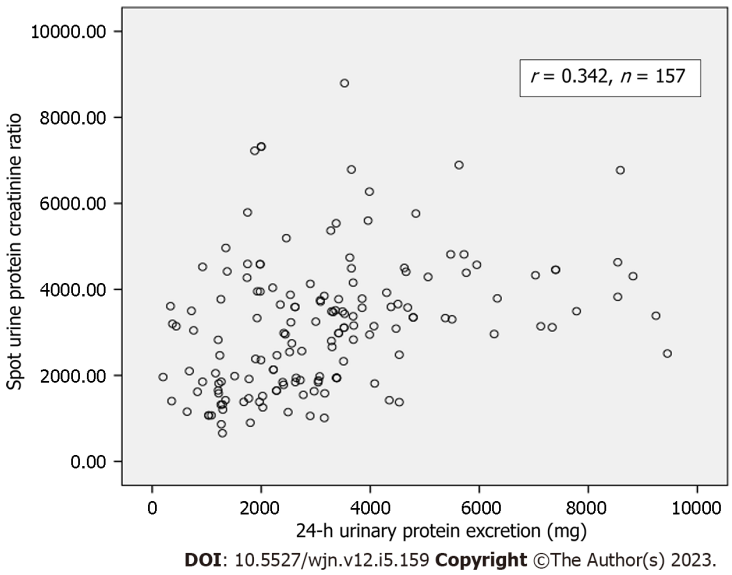

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Figure 1 Correlation between spot urine protein-to-creatinine ratio and 24-h urinary protein excretion in all patients (*n* = 157).

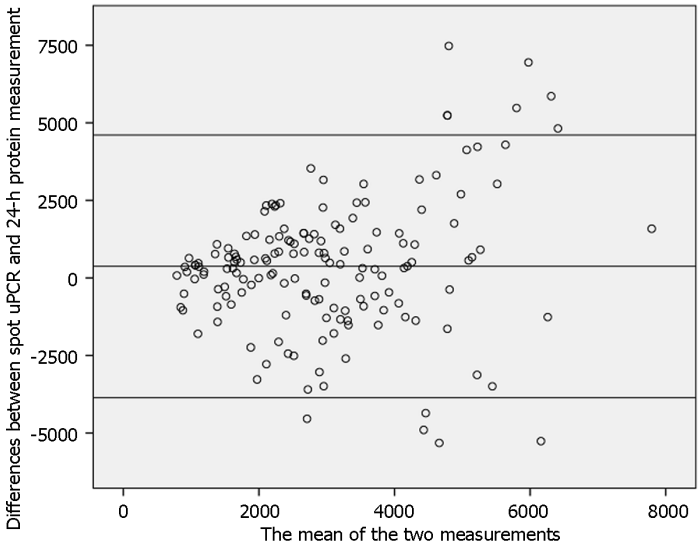

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Figure 2 Bland and Altman plot comparing the differences between spot urine protein-to-creatinine ratio and 24-h protein measurement against the mean of the measurement by the two methods. The mean bias is 373 mg; however, the limits of agreement are fairly wide (from -3682 to 4069 mg), particularly as the mean of the two methods rises.

significant (P = 0.058). There were 13 patients in our group who had protein excretion in excess of 6000 mg and after excluding them from the group of 78 patients with protein excretion ≥ 3000 mg, the correlation with spot uPCR (r = 0.295) became significant (P = 0.02). Similarly, there were 12 patients in the group with protein excretion < 3000 mg who had proteinuria of less than 1000 mg, and after excluding them from this group, when we recalculated the correlation with spot uPCR it remained weak (r = 0.21).

As is well known, uPCR is also influenced by gender, as females have lower creatinine excretion due to lower muscle mass and this can give rise to a higher ratio compared to males for a similar degree of proteinuria. However, the correlation was not much different when we stratified the entire group according to gender. Besides the degree of proteinuria and gender, uPCR is also influenced by renal function, the timing of random (spot) urine specimens, and the handling of urine samples[10,11]. The mean creatinine clearance in this study population was 75 mL/minute, and 75% of the population had serum creatinine less than 1.23 mg/dL; therefore it is unlikely that the ratio was influenced by compromised renal functions. Patients were asked to submit spot urine samples on the following day of 24-h urine collection, but this sample was taken at different times of day in individual patients and physical activity may have influenced protein excretion in some patients who had come late for submitting their specimens.

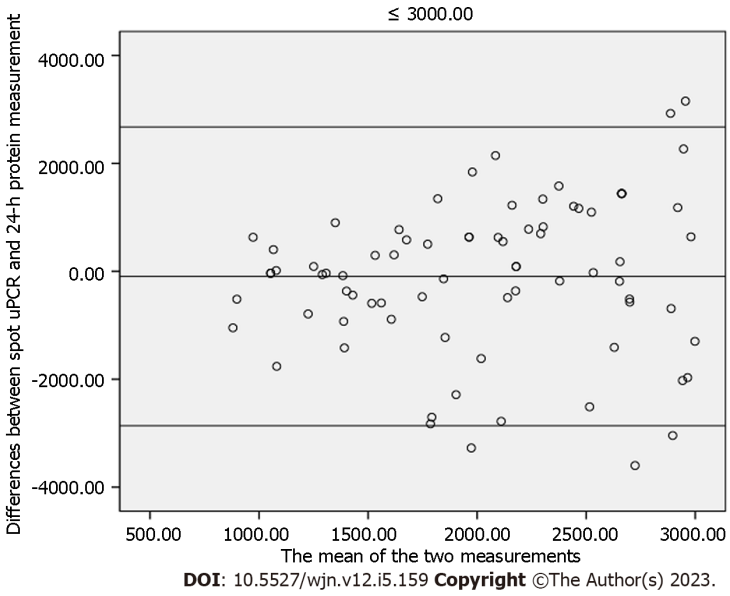

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Figure 3 The mean bias and limits of agreement in the group of patients with protein excretion of less than 3000 mg. The mean bias is -93.64 mg and the limits of agreement are -2861.53 to 2674.25 mg in this group of patients.

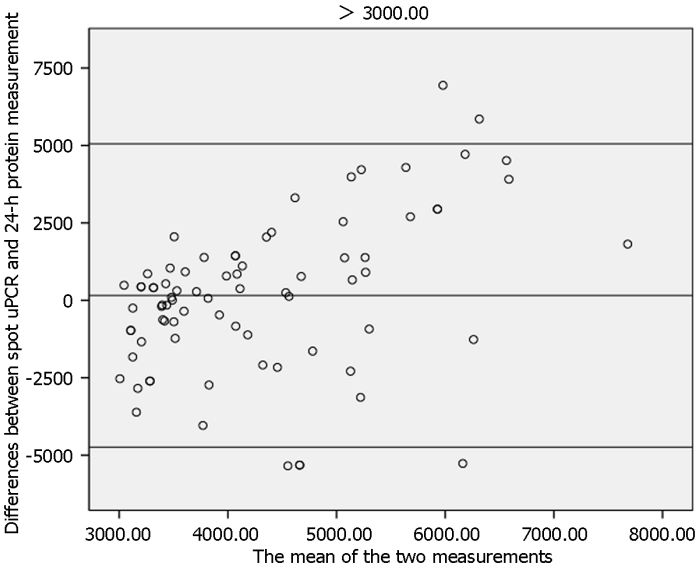

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Figure 4 The mean bias and limits of agreement in the group of patients with more than 3000 mg protein excretion. The mean bias is 158.36 mg and the limits of agreement are -4738.46 to 5035.18 mg in this group of patients.

One possible explanation for the poor correlation between uPCR and 24-h urinary protein measurement is that the latter assumes a creatinine excretion of 1000 mg/d which may be incorrect in some populations[6]. Around 50% of our population had a BMI of < 21.5 kg/m^2 suggesting low muscle mass and hence low creatinine excretion. Indeed, when we analyzed the correlation between spot uPCR and 24-h urine protein excretion in the group of patients with BMI >25 kg/m^2, we observed a much stronger correlation than patients with lower BMI (r = 0.45, P = 0.003).

More important than correlation from the clinical perspective is the degree of agreement or the difference between two measurements. To replace 24-h measurement with uPCR in spot urine samples for clinical decision-making, it is prudent to see whether the two techniques agree sufficiently. In this study, the limits of agreement were fairly wide, more so with higher grades of proteinuria. Irrespective of the fact that whether proteinuria was sub-nephrotic or in the nephrotic range, these differences are unacceptable. In an earlier study of 170 proteinuric patients, good agreement between the two methods was reported in the range between 200 mg and 3.5 g protein excretion[22]. A meta-analysis of 13 studies in patients with systemic lupus erythematosus showed poor agreement between the two methods[23]. In a study using NEPTUNE cohort of patients, there was modest correlation between the two methods, and both correlation and predictability improved on Log10 transformation of values[24]. Only 25% of patients in NEPTUNE cohort had nephrotic syndrome, making it difficult to generalize it for higher grades of proteinuria. Lately, in a single center study of 142

proteinuric patients, a poor agreement was reported between 24-h urine protein excretion and uPCR from different timed spot samples. The limits of agreement were widest when protein excretion exceeded 3.5 g in 24 h (-3.2 to 8.2)[25].

Our study has certain limitations. It is a single center and single laboratory-based study. We used uPCR rather than albumin: Creatinine ratio, which is more reliable compared to uPCR. Spot urine samples were taken at different times of day in individual patients which may have affected protein excretion and hence its concentration. Some patients were already on steroids, which causes sarcopenia and decreases creatinine excretion resulting in higher uPCR. Moreover, specific disease diagnoses were not recorded in this study. Some of the patients might have had non-glomerular pathology. The main strength of our study is the broad range of proteinuria used for comparison, with a nearly equal number of patients below and above the nephrotic threshold of proteinuria. The spot urine sample was collected on the very next day of 24-h urine collection so that both represented similar pathophysiology. Although 24-h urine protein excretion is considered the gold standard test for accurate estimation of proteinuria, over-collection and under-collection of urine sample affects its accuracy[26-28]. We tried to mitigate this issue by excluding patients who had creatinine excretion outside the expected range based on their weight.

CONCLUSION

In conclusion, considering the overall poor correlation and the wide limits of agreement between 24-h urine protein excretion and uPCR, the latter should be used with great caution to predict protein excretion in patients with glomerular disease. This is more so when important therapeutic decisions are being made based on the degree of proteinuria.

ARTICLE HIGHLIGHTS

Research background

There are a number of methods by which the quantification of protein excretion in urine is done to inform clinical decisions. Among these, the estimation of protein excretion in the 24-h urinary sample is the traditional and gold standard method. However, it is cumbersome, time-consuming, and prone to errors. The alternative method of measuring urine protein-to-creatinine ratio (uPCR) is used widely in clinical practice as it is quick, patient-friendly, and reliable. The available data on the correlation between the above two methods is controversial.

Research motivation

We also heavily rely on uPCR for our routine patient care. However, we do not know how it correlates with 24-h urinary protein excretion. This motivated us to determine the correlation and degree of agreement between the two tests, so that we should use uPCR results accordingly.

Research objectives

The objectives of this study were to determine the correlation of spot uPCR with 24-h urinary protein excretion test and in particular, the degree of agreement between the two tests, in patients suffering from various forms of glomerulopathies so that we may use this test with caution in future.

Research methods

This was a cross-sectional, observational study conducted on all newly presenting adult patients (age: 18 to 60 years) with proteinuria who were being investigated for suspected glomerulonephritis (GN). All patients were counseled regarding 24-h urine collection. A spot urine sample was collected the next day at the time of submission of a 24-h urine sample for measuring uPCR along with a blood sample. SPSS version 20.0 was used for statistical analysis.

Research results

A total of 157 patients with a mean age of 30.45 ± 12.11 years were included. There were 94 (59.8%) males and 63 (40.2%) females. The mean 24-h urinary protein excretion was 3192.78 ± 1959.79 mg and the mean spot uPCR was 3.16 ± 1.52 in all patients. A significant but poor correlation was observed between spot uPCR and 24-h urinary protein excretion (r = 0.342, P = 0.01) among all patients. On subgroup analysis, a slightly better correlation was found in patients older than 47 years (r = 0.78), and those with body mass index > 25 kg/m^2 (r = 0.45). Bland and Altman's plot analysis of the two tests also showed a wide range of the limits of agreement between the two methods.

Research conclusions

The results from this study show a significant, positive but poor correlation between spot uPCR and 24-h urinary protein estimation in various types of glomerular diseases. The agreement between the two methods was also poor. Hence, there is a need for careful interpretation of the ratio in an unselected group of patients with glomerular diseases.

Research perspectives

There is a need to conduct a well-planned, international, multi-center study to resolve the controversy of correlation and agreement between the two most widely used methods of proteinuria estimation in clinical practice.

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FOOTNOTES

Author contributions: Raza A and Ahmed E contributed equally to this work; Raza A, Nawaz SH, Rashid R, Ahmed E, and Mubarak M designed the research study; Raza A, Nawaz SH and Rashid R performed the research; Raza A, Ahmed E, and Mubarak M analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Sindh Institute of Urology and Transplantation (Pakistan).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: The dataset and related documents are available from the corresponding author at [dramber88@gmail.com]. Consent was not obtained but the presented data are anonymized and risk of identification is low.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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L-Editor: A
P-Editor: Chen YX

REFERENCES

1 **Ahmed PI**, Islam MN, Alam MB, Bhuiya FK, Noman MU, Chowdhury MN. Comparison of 24-Hour Urinary Protein and Spot Urinary Protein- Creatinine Ratio in the Assessment of Proteinuria in Patients with Glomerulonephritis. *J Dhaka Med Coll* 2015; **23**: 194-202 [DOI: 10.3329/jdmc.v23i2.25390]
2 **Antunes VV**, Veronese FJ, Morales JV. Diagnostic accuracy of the protein/creatinine ratio in urine samples to estimate 24-h proteinuria in patients with primary glomerulopathies: a longitudinal study. *Nephrol Dial Transplant* 2008; **23**: 2242-2246 [PMID: 18281321 DOI: 10.1093/ndt/gfm949]
3 **Patil P**, Shah V, Shah B. Comparison of spot urine protein creatinine ratio with 24 hour urine protein for estimation of proteinuria. *J Assoc Physicians India* 2014; **62**: 406-410 [PMID: 25438486]
4 **Wahbeh AM**, Ewais MH, Elsharif ME. Comparison of 24-hour urinary protein and protein-to-creatinine ratio in the assessment of proteinuria. *Saudi J Kidney Dis Transpl* 2009; **20**: 443-447 [PMID: 19414948]
5 **Kamińska J**, Dymicka-Piekarska V, Tomaszewska J, Matowicka-Karna J, Koper-Lenkiewicz OM. Diagnostic utility of protein to creatinine ratio (P/C ratio) in spot urine sample within routine clinical practice. *Crit Rev Clin Lab Sci* 2020; **57**: 345-364 [PMID: 32058809 DOI: 10.1080/10408363.2020.1723487]
6 **Ginsberg JM**, Chang BS, Matarese RA, Garella S. Use of single voided urine samples to estimate quantitative proteinuria. *N Engl J Med* 1983; **309**: 1543-1546 [PMID: 6656849 DOI: 10.1056/NEJM198312223092503]
7 **Montero N**, Soler MJ, Pascual MJ, Barrios C, Márquez E, Rodríguez E, Berrada A, Riera M, Coca L, Orfila MA, Pascual J. Correlation between the protein/creatinine ratio in spot urine and 24-hour urine protein. *Nefrologia* 2012; **32**: 494-501 [PMID: 22806284 DOI: 10.3265/Nefrologia.pre2012.Apr.11300]
8 **Yang CY**, Chen FA, Chen CF, Liu WS, Shih CJ, Ou SM, Yang WC, Lin CC, Yang AH. Diagnostic Accuracy of Urine Protein/Creatinine Ratio Is Influenced by Urine Concentration. *PLoS One* 2015; **10**: e0137460 [PMID: 26353117 DOI: 10.1371/journal.pone.0137460]
9 **Chen CF**, Yang WC, Yang CY, Li SY, Ou SM, Chen YT, Shih CJ, Chien CC, Chen MC, Wang YJ, Lin CC. Urinary protein/creatinine ratio weighted by estimated urinary creatinine improves the accuracy of predicting daily proteinuria. *Am J Med Sci* 2015; **349**: 477-487 [PMID: 25992536 DOI: 10.1097/MAJ.0000000000000488]
10 **Methven S**, MacGregor MS. Empiricism or rationalism: how should we measure proteinuria? *Ann Clin Biochem* 2013; **50**: 296-300 [PMID:

23787260 DOI: 10.1177/0004563212473283]
11 **Naresh CN**, Hayen A, Craig JC, Chadban SJ. Day-to-day variability in spot urine protein-creatinine ratio measurements. *Am J Kidney Dis* 2012; **60**: 561-566 [PMID: 22591781 DOI: 10.1053/j.ajkd.2012.04.010]
12 **Price CP**, Newall RG, Boyd JC. Use of protein:creatinine ratio measurements on random urine samples for prediction of significant proteinuria: a systematic review. *Clin Chem* 2005; **51**: 1577-1586 [PMID: 16020501 DOI: 10.1373/clinchem.2005.049742]
13 **Ali A**, Asif N, Yaqub S, Kashif W, Merchant D, Yazdant I. Spot urine protein: creatinine ratio versus 24 hour urine protein at various levels of GFR patients referred to a tertiary care hospital of Pakistan. *J Pak Med Assoc* 2008; **58**: 476-479 [PMID: 18846792]
14 **Khan DA**, Ahmad TM, Qureshil AH, Halim A, Ahmad M, Afzal S. Assessment of proteinuria by using protein: creatinine index in random urine sample. *J Pak Med Assoc* 2005; **55**: 428-431 [PMID: 16304850]
15 **Jafar TH**, Chaturvedi N, Hatcher J, Levey AS. Use of albumin creatinine ratio and urine albumin concentration as a screening test for albuminuria in an Indo-Asian population. *Nephrol Dial Transplant* 2007; **22**: 2194-2200 [PMID: 17405790 DOI: 10.1093/ndt/gfm114]
16 **Jafar TH**, Schmid CH, Levey AS. Serum creatinine as marker of kidney function in South Asians: a study of reduced GFR in adults in Pakistan. *J Am Soc Nephrol* 2005; **16**: 1413-1419 [PMID: 15800118 DOI: 10.1681/ASN.2004121100]
17 **Jafar TH**, Chaturvedi N, Gul A, Khan AQ, Schmid CH, Levey AS. Ethnic differences and determinants of proteinuria among South Asian subgroups in Pakistan. *Kidney Int* 2003; **64**: 1437-1444 [PMID: 12969163 DOI: 10.1046/j.1523-1755.2003.00212.x]
18 **Schultz CJ**, Dalton RN, Turner C, Neil HA, Dunger DB. Freezing method affects the concentration and variability of urine proteins and the interpretation of data on microalbuminuria. The Oxford Regional Prospective Study Group. *Diabet Med* 2000; **17**: 7-14 [PMID: 10691153 DOI: 10.1046/j.1464-5491.2000.00200.x]
19 **Ruggenenti P**, Gaspari F, Perna A, Remuzzi G. Cross sectional longitudinal study of spot morning urine protein:creatinine ratio, 24 hour urine protein excretion rate, glomerular filtration rate, and end stage renal failure in chronic renal disease in patients without diabetes. *BMJ* 1998; **316**: 504-509 [PMID: 9501711 DOI: 10.1136/bmj.316.7130.504]
20 **Radhakrishnan J**, Cattran DC. The KDIGO practice guideline on glomerulonephritis: reading between the (guide)lines--application to the individual patient. *Kidney Int* 2012; **82**: 840-856 [PMID: 22895519 DOI: 10.1038/ki.2012.280]
21 **Methven S**, MacGregor MS, Traynor JP, O'Reilly DS, Deighan CJ. Assessing proteinuria in chronic kidney disease: protein-creatinine ratio versus albumin-creatinine ratio. *Nephrol Dial Transplant* 2010; **25**: 2991-2996 [PMID: 20237054 DOI: 10.1093/ndt/gfq140]
22 **Chitalia VC**, Kothari J, Wells EJ, Livesey JH, Robson RA, Searle M, Lynn KL. Cost-benefit analysis and prediction of 24-hour proteinuria from the spot urine protein-creatinine ratio. *Clin Nephrol* 2001; **55**: 436-447 [PMID: 11434354]
23 **Medina-Rosas J**, Yap KS, Anderson M, Su J, Touma Z. Utility of Urinary Protein-Creatinine Ratio and Protein Content in a 24-Hour Urine Collection in Systemic Lupus Erythematosus: A Systematic Review and Meta-Analysis. *Arthritis Care Res (Hoboken)* 2016; **68**: 1310-1319 [PMID: 26714024 DOI: 10.1002/acr.22828]
24 **Hogan MC**, Reich HN, Nelson PJ, Adler SG, Cattran DC, Appel GB, Gipson DS, Kretzler M, Troost JP, Lieske JC. The relatively poor correlation between random and 24-hour urine protein excretion in patients with biopsy-proven glomerular diseases. *Kidney Int* 2016; **90**: 1080-1089 [PMID: 27528553 DOI: 10.1016/j.kint.2016.06.020]
25 **Rydzewska-Rosołowska A**, Kakareko K, Naumnik B, Hryszko T. Comparison of Different Methods of Urinary Protein Excretion Measurement: Is the King Really Dead? *Kidney Blood Press Res* 2019; **44**: 993-1001 [PMID: 31454803 DOI: 10.1159/000501884]
26 **Selvarajah V**, Flynn R, Isles C. Comparison of estimated protein output and urine protein: creatinine ratio in first and second voids with 24-hour urine protein. *Nephron Extra* 2011; **1**: 235-241 [PMID: 22470397 DOI: 10.1159/000333474]
27 **Morales JV**, Weber R, Wagner MB, Barros EJ. Is morning urinary protein/creatinine ratio a reliable estimator of 24-hour proteinuria in patients with glomerulonephritis and different levels of renal function? *J Nephrol* 2004; **17**: 666-672 [PMID: 15593033]
28 **Akin D**, Ozmen S. An unresolved issue: The relationship between spot urine protein-to-creatinine ratio and 24-hour proteinuria. *J Int Med Res* 2019; **47**: 1179-1184 [PMID: 30621497 DOI: 10.1177/0300060518819602]

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ORIGINAL ARTICLE

Observational Study

Antihypertensive prescribing patterns in non-dialysis dependent chronic kidney disease: Findings from the Salford Kidney Study

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Abstract

BACKGROUND

Hypertension is commonly observed in patients living with chronic kidney disease (CKD). Finding an optimal treatment regime remains challenging due to the complex bidirectional cause-and-effect relationship between hypertension and CKD. There remains variability in antihypertensive treatment practices.

AIM

To analyze data from the Salford Kidney Study database in relation to antihypertensive prescribing patterns amongst CKD patients.

METHODS

The Salford Kidney Study is an ongoing prospective study that has been recruiting CKD patients since 2002. All patients are followed up annually, and their medical records including the list of medications are updated until they reach study endpoints [starting on renal replacement therapy or reaching estimated glomerular filtration rate (eGFR) expressed as mL/min/1.73 m^2 ≤ 10 mL/min/1.73 m^2, or the last follow-up date, or data lock on December 31, 2021, or death]. Data on antihypertensive prescription practices in correspondence to baseline eGFR, urine albumin-creatinine ratio, primary CKD aetiology, and cardiovascular disease were evaluated. Associations between patients who were

prescribed three or more antihypertensive agents and their clinical outcomes were studied by Cox regression analysis. Kaplan-Meier analysis demonstrated differences in survival probabilities.

RESULTS

Three thousand two hundred and thirty non-dialysis-dependent CKD patients with data collected between October 2002 and December 2019 were included. The median age was 65 years. A greater proportion of patients were taking three or more antihypertensive agents with advancing CKD stages (53% of eGFR ≤ 15 mL/min/1.73 m^2 *vs* 26% of eGFR ≥ 60 mL/min/1.73 m^2, $P < 0.001$). An increased number of patients receiving more classes of antihypertensive agents was observed as the urine albumin-creatinine ratio category increased (category A3: 62% *vs* category A1: 40%, $P < 0.001$), with the upward trends particularly noticeable in the number of individuals prescribed renin angiotensin system blockers. The prescription of three or more antihypertensive agents was associated with all-cause mortality, independent of blood pressure control (hazard ratio: 1.15; 95% confidence interval: 1.04-1.27, $P = 0.006$). Kaplan-Meier analysis illustrated significant differences in survival outcomes between patients with three or more and those with less than three antihypertensive agents prescribed (log-rank, $P < 0.001$).

CONCLUSION

Antihypertensive prescribing patterns in the Salford Kidney Study based on CKD stage were consistent with expectations from the current United Kingdom National Institute of Health and Care Excellence guideline algorithm. Outcomes were poorer in patients with poor blood pressure control despite being on multiple antihypertensive agents. Continued research is required to bridge remaining variations in hypertension treatment practices worldwide.

Key Words: Hypertension; Chronic kidney disease; Antihypertensive agents; Prescribing patterns; Cardiovascular complications; Renin angiotensin system blockers

Core Tip: This is an observational study that prospectively evaluated antihypertensive prescribing patterns in 3230 non-dialysis chronic kidney disease (CKD) patients over a 20-year period. Antihypertensive prescribing patterns based on CKD stage were consistent with expectations from the United Kingdom National Institute of Health and Care Excellence guideline algorithm and other international guidelines in relation to hypertension management in CKD.

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INTRODUCTION

Chronic kidney disease (CKD) is a progressive disease defined by the presence of structural or functional abnormalities within the kidney for 3 mo or more according to the Kidney Disease Improving Global Outcomes (KDIGO)[1]. Touted as an emerging public health issue of the 21st century, the prevalence of CKD is exponentially growing and is projected to become the fifth-leading cause of mortality globally by 2040[2]. The aetiology of CKD is multidimensional and complex, of which there are various causes and consequences[3-5]. Other than diabetes mellitus, hypertension is a major contributor towards the progression of CKD and a leading consequence of CKD[6]. Depending on the stage of CKD, the prevalence of hypertension in CKD populations varies (ranging between 67% and 92%, according to previously published data), but the majority of patients with CKD are likely to have hypertension[7,8]. Given the potential health consequences of hypertension over time, namely its associated cardiovascular risks and risk of further kidney damage, adequate control of blood pressure (BP) in the CKD population is of vital importance to improve clinical outcomes[9,10].

It is not known to what extent clinicians adopt guideline-recommended or preferred antihypertensive treatment approaches for their CKD patients in the real-world setting[7,11]. Previous electronic health record and prospective longitudinal studies noted clinicians primarily prescribed angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) for CKD patients with hypertension, but varying combinations of antihypertensive prescription over time was noted when all antihypertensive agents are considered[12-16]. It remains largely unestablished which combination(s) of antihypertensive agents would generate the best results in terms of BP control and other clinical outcomes. Aiming to address these unknowns, our study evaluated trends and patterns relating to antihypertensive prescription over a 20-year period in patients identified with non-dialysis-dependent CKD included in the Salford Kidney Study (SKS).

MATERIALS AND METHODS

Study cohort

Our investigation was conducted on patients enrolled in the non-dialysis-dependent CKD arm of the SKS (SKS-CKD). The SKS-CKD is an ongoing long-term prospective observational study that has been recruiting patients with CKD since the year 2002. Details of study recruitment in the SKS have been described in previously published literature[17,18]. In brief, any CKD patient above the age of 18 years and able to provide informed consent is recruited. At study baseline (*i.e.* date of recruitment), data including demographic information, comorbidities, physical parameters (weight, height, BP, heart rate, *etc*) and a detailed medication history is recorded. The patients are then followed up annually to update their comorbidity status and medication list until they reach a study endpoint [which may include death, starting on renal replacement therapy (RRT), reaching estimated glomerular filtration rate (eGFR) ≤ 10 mL/min/1.73 m^2, the last follow-up date, or data lock of December 31, 2021 for this study]. All haematological and biochemical variables at study and routine clinic visits are recorded from electronic patient records.

Study definitions

In the SKS, hypertensive status was defined as being on antihypertensive agents or recorded as having a history of hypertension in general practitioner records. A smoking history was defined as current or past history of smoking, and a similar definition was followed in the collection of alcohol history. Body mass index was calculated using weight in kilograms and height in meters (kg/m^2). End stage kidney disease (ESKD) was defined as starting on RRT or reaching an eGFR ≤ 10 mL/min/1.73 m^2 for patients who opted for conservative care. We defined renin angiotensin system (RAS) blockers as being ACEI or ARB or renin inhibitors.

Data and statistical analysis

The baseline characteristics of the cohort were grouped based on CKD stages (categorized by eGFR) and proteinuria [categorized by urine albumin-creatinine ratio (uACR)]. uACR was calculated from urine protein-creatinine ratio (uPCR). This involved initial conversion from mg/mmol to mg/g by multiplication of 8.84, and further conversion from uPCR (uPCR: the standard measure in this real world population) to uACR as per the standardized formula in the kidney failure risk equation[19].

Prescription patterns of antihypertensive agents at baseline were presented corresponding to eGFR categories, uACR categories, primary kidney disease aetiology, and cardiovascular disease. Antihypertensive agent(s) prescribing trends were also examined at the 12-mo and 24-mo follow-up.

When presenting results from our statistical analyses, continuous variables were expressed with the median value (interquartile range). After checking for the normality of distribution, the *P* value was calculated by the Kruskal-Wallis H test. Categorical variables are expressed as frequencies in absolute number form (percentage), with *P* values calculated by the χ^2 test. The association between being prescribed three or more antihypertensive agents and clinical outcomes (*i.e.* all-cause mortality and reaching ESKD) was studied by univariate and multivariate Cox regression analysis. The multivariable models were developed by including variables in a stepwise manner. Kaplan-Meier analysis was used to demonstrate the differences in survival probabilities, with the log-rank test used to calculate the *P* values. The annual rate of decline in eGFR (delta eGFR) was calculated using all available eGFRs between the study baseline and endpoints by linear regression analysis. Only patients with three or more eGFRs and at least 1 year of follow-up data were included in the delta eGFR analysis. All statistical analyses were performed using IBM SPSS Version 26, registered with the University of Manchester.

Ethical considerations

The SKS received ethical approval for all of the observational studies conducted in relation to its database, with individual patient consent. The research ethics number is 15/NW/0818.

RESULTS

Baseline characteristics

A total of 3230 patients with complete datasets were included in this analysis. The median age of the cohort was 65 years with a predominance of the male sex (60%) and those of white ethnicity (96%). At baseline, the majority of study participants (66%) had an eGFR between 15 and 45 mL/min/1.73 m^2. As baseline eGFR declined, the median systolic BP of the cohort was noted to have increased, and a higher proportion of those with lower eGFR also had a history of hypertension, diabetes, and cardiovascular events ($P < 0.001$). Biochemical variables showed decreases in haemoglobin and calcium levels and increases in phosphate levels in correspondence to worsening eGFR ($P < 0.001$) (Table 1).

Distribution of antihypertensive agent prescription practices based on eGFR and primary kidney disease aetiology

Amongst patient groups with a lower eGFR, there were greater proportions that were receiving three or more antihypertensive agents (53% of eGFR ≤ 15 mL/min/1.73 m^2 *vs* 26% of eGFR ≥ 60 mL/min/1.73 m^2, $P < 0.001$). The most prescribed antihypertensive agents were RAS blockers (61%), followed by diuretics (47%), dihydropyridine calcium channel blockers (CCB) (39%), and beta blockers (34%). Alpha-blockers were also a popularly prescribed antihypertensive and prescribed more frequently in lower eGFR ranges. The proportion of patients receiving RAS blockers decreased with a lower eGFR,

Table 1 Demographic information and baseline characteristics of the cohort based on estimated glomerular filtration rate categories

Demographic variables	eGFR ≥ 60, *n* = 218[1]	eGFR 45-59, *n* = 491[1]	eGFR 30-45, *n* = 962[1]	eGFR 15-29, *n* = 1174[1]	eGFR < 15, *n* = 385[1]	Total, *n* = 3230[1]	*P* value[1]
Age, yr	53 (44-63)	62 (50-70)	68 (56-75)	70 (60-78)	71 (60-78)	67 (56-76)	< 0.001
Sex, male	126 (57.8)	308 (62.7)	573 (59.6)	691 (58.9)	251 (65.2)	1949 (60.3)	0.143
Ethnicity, white	198 (90.8)	467 (95.1)	924 (99.6)	1127 (96.0)	375 (97.4)	3091 (95.7)	0.003
BMI, kg/m^2	28.3 (24.6-33.2)	28.2 (25.0-32.4)	28.0 (25.0-32.4)	28.0 (25.0-32.6)	27.4 (24.0-33.0)	28.0 (24.7-32.6)	0.490
Systolic BP, mmHg	132 (120-148)	135 (122-150)	139 (125-153)	140 (126-155)	143 (130-160)	139 (125-154)	< 0.001
Diastolic BP, mmHg	76 (70-82)	76 (68-82)	75 (67-81)	72 (65-80)	75 (66-82)	75 (66-81)	0.001
Smoking history	124 (56.9)	300 (61.1)	630 (65.5)	781 (65.5)	255 (66.2)	2090 (64.7)	0.027
Alcohol history	121 (55.5)	252 (51.3)	465 (48.3)	504 (42.9)	149 (38.7)	1491 (46.2)	< 0.001
Hypertension	166 (76.1)	414 (84.3)	862 (89.6)	1091 (92.9)	362 (94.0)	2895 (89.6)	< 0.001
Diabetes mellitus	37 (17.0)	109 (22.2)	291 (30.2)	456 (38.8)	148 (38.4)	1041 (32.2)	< 0.001
IHD	21 (9.6)	75 (15.3)	221 (23.0)	275 (23.4)	75 (19.5)	667 (20.7)	< 0.001
MI	14 (6.4)	61 (12.4)	149 (15.5)	199 (17.0)	59 (15.3)	482 (14.9)	0.001
CCF	18 (8.3)	52 (10.6)	169 (17.6)	233 (19.8)	84 (21.8)	556 (17.2)	< 0.001
CVA	8 (3.7)	25 (5.1)	75 (7.8)	100 (8.5)	41 (10.6)	249 (7.7)	0.004
PVD	19 (8.7)	47 (9.6)	122 (12.7)	169 (14.4)	58 (15.1)	415 (12.8)	0.016
COPD	32 (14.7)	74 (15.1)	179 (18.6)	219 (18.7)	64 (16.6)	568 (17.6)	0.260
CLD	8 (3.7)	19 (3.9)	30 (3.1)	33 (2.8)	9 (2.3)	99 (3.1)	0.683
Malignancy	19 (8.7)	39 (7.9)	109 (11.3)	136 (11.6)	50 (13.0)	353 (10.9)	0.094
Laboratory variables							
Haemoglobin, g/L	134 (121-145)	131 (120-141)	126 (115-137)	120 (110-130)	113 (104-122)	123 (112-135)	< 0.001
Albumin, g/L	44 (41-46)	43 (41-45)	43 (40-45)	42 (40-44)	42 (39-44)	43 (40-45)	< 0.001
Corrected calcium, mmol/L	2.32 (2.22-2.40)	2.33 (2.24-2.41)	2.31 (2.23-2.39)	2.30 (2.20-2.39)	2.28 (2.17-2.37)	2.31 (2.22-2.39)	< 0.001
Phosphate, mmol/L	1.05 (0.91-1.10)	1.03 (0.91-1.16)	1.07 (0.95-1.21)	1.16 (1.02-1.31)	1.39 (1.21-1.59)	1.12 (0.98-1.29)	< 0.001
ALP, U/L	71 (57-85)	76 (59-97)	82 (66-102)	86 (69-112)	89 (69-111)	83 (66-105)	< 0.001
uACR, mg/g[2]	15.9 (8.3-57.2)	21.0 (10.6-60.5)	24.0 (11.7 -77.0)	43.0 (16.4-132.7)	106.5 (44.4-232.6)	32.7 (13.4-111.1)	< 0.001

[1]Continuous variables are expressed with the median value (interquartile range). The *P* values were calculated by the Kruskal Wallis H test. Categorical variables are expressed as numbers (percentage). The *P* values were calculated by the χ^2 test.
[2]Missing urine albumin-creatinine ratio values for 391 patients.
ALP: Alkaline phosphatase; BMI: Body mass index; BP: Blood pressure; CCF: Congestive cardiac failure; CLD: Chronic liver disease; COPD: Chronic obstructive pulmonary disease; CVA: Cerebrovascular accidents; eGFR: Estimated glomerular filtration rate expressed as mL/min/1.73 m^2; IHD: Ischemic heart disease; MI: Myocardial infarction; PVD: Peripheral vascular disease; uACR: Urine albumin-creatinine ratio.

whereas the proportion on diuretics, dihydropyridine CCBs, and beta blockers increased ($P < 0.001$) (Table 2).

Furthermore, the distribution of antihypertensive agent prescriptions for patients across the spectrum of primary kidney disease aetiologies illustrated that RAS blockers were the predominant agents for most diagnoses, followed by diuretics and dihydropyridine CCBs (Table 3).

Distribution of antihypertensive agent prescription practices based on uACR and cardiovascular comorbidity

A greater proportion of patients were receiving three or more antihypertensive agents with each higher uACR category (category A1: 40% *vs* category A2: 43% *vs* category A3: 62%, $P < 0.001$). There was a trend of increased numbers of individuals prescribed ACEI or ARB (Table 4).

When comparing between patients with and without a history of congestive cardiac failure (CCF), diuretics (68% *vs* 43%, $P < 0.001$), potassium-sparing diuretics (spironolactone or eplerenone) (10% *vs* 2%, $P < 0.001$), and beta blockers (45% *vs* 32%, $P < 0.001$) were prescribed more frequently amongst those diagnosed with CCF. Similar prescription patterns were noted for any other form of cardiovascular disease. Interestingly, there were no significant differences in the pattern of prescription of RAS blockers alone, based on cardiovascular disease status (Table 5).

Table 2 Number of patients prescribed each antihypertensive class at baseline, organized by estimated glomerular filtration rate categories at baseline

Antihypertensive class	eGFR > 60, *n* = 218[1]	eGFR 45-59, *n* = 491[1]	eGFR 30-45, *n* = 962[1]	eGFR 15-29, *n* = 1174[1]	eGFR < 15, *n* = 385[1]	Total, *n* = 3230[1]	*P* value[1]
None	54 (24.8)	73 (14.9)	97 (10.1)	78 (6.6)	26 (6.8)	328 (10.2)	< 0.001
Three or more agents	57 (26.1)	158 (32.2)	397 (41.3)	565 (48.1)	206 (53.5)	1383 (42.8)	< 0.001
Diuretic (thiazide and loop)	58 (26.6)	172 (35.0)	441 (45.8)	641 (54.6)	213 (55.3)	1525 (47.2)	< 0.001
CCB (dihydropyridine)	58 (26.6)	149 (30.3)	364 (37.8)	480 (40.9)	205 (53.2)	1256 (38.9)	< 0.001
CCB (non-dihydropyridine)	6 (2.8)	11 (2.2)	44 (4.6)	50 (4.3)	23 (6.0)	134 (4.1)	0.055
Beta-blocker	51 (23.4)	133 (27.1)	324 (33.7)	443 (37.7)	156 (40.5)	1107 (34.3)	< 0.001
Alpha-blocker	28 (12.8)	72 (14.7)	186 (19.3)	335 (28.5)	158 (41.0)	779 (24.1)	< 0.001
Central agents	9 (4.1)	15 (3.1)	34 (3.5)	59 (5.0)	33 (8.6)	150 (4.6)	0.001
Vasodilators	2 (0.9)	2 (0.4)	6 (0.6)	13 (1.1)	7 (1.8)	30 (0.9)	0.189
RAS blocker	126 (57.8)	316 (64.4)	616 (64.0)	733 (62.4)	192 (50.0)	1983 (61.4)	< 0.001
Dual RAS blockers	22 (10.1)	34 (7.0)	50 (5.2)	67 (5.7)	14 (31.6)	187 (5.8)	0.014
Spironolactone/eplerenone	7 (3.2)	17 (3.5)	36 (3.7)	44 (3.7)	8 (2.1)	112 (3.5)	0.599

[1]Absolute number for frequencies (percentage). The *P* values were calculated by the χ^2 test.
CCB: Calcium channel blocker; eGFR: estimated glomerular filtration rate expressed as mL/min/1.73 m^2; RAS: Renin angiotensin system.

Table 3 Number of patients prescribed each antihypertensive class at baseline, organised by primary aetiology of chronic kidney disease at baseline

Primary aetiology of CKD	Three or more[1]	RAS blocker[1]	Diuretic[1]	Beta blocker[1]	Alpha blocker[1]	CCB (dihydropyridine)[1]	CCB (non-dihydropyridine)[1]	Central agents[1]
Diabetes, *n* = 636	386 (61)	463 (73)	416 (65)	239 (38)	220 (35)	281 (44)	32 (5)	53 (8)
Hypertension, *n* = 471	246 (52)	294 (62)	245 (52)	210 (45)	154 (33)	222 (47)	33 (7)	21 (5)
Renovascular disease, *n* = 256	163 (64)	142 (56)	178 (70)	121 (47)	92 (36)	122 (48)	20 (8)	27 (11)
Pyelonephritis, *n* = 200	40 (20)	102 (51)	54 (27)	50 (25)	23 (12)	61 (31)	4 (2)	3 (2)
ADPKD, *n* = 197	66 (34)	149 (76)	69 (35)	55 (28)	40 (20)	78 (40)	2 (1)	6 (3)
Tubulointerstitial nephritis, *n* = 116	9 (8)	40 (35)	18 (16)	27 (23)	8 (7)	35 (30)	3 (3)	2 (20)
Glomerulonephritis, *n* = 375	171 (46)	305 (81)	174 (46)	95 (25)	73 (20)	147 (39)	9 (2)	21 (6)
Vasculitis, *n* = 118	31 (26)	61 (52)	34 (29)	35 (30)	19 (16)	40 (34)	2 (2)	1 (1)
Haematological disease, *n* = 31	8 (26)	14 (45)	9 (29)	8 (26)	4 (13)	7 (23)	0	1 (3)
Other/unknown aetiology, *n* = 830	263 (32)	413 (50)	328 (40)	267 (32)	146 (18)	263 (32)	29 (4)	15 (2)

[1]Absolute number for frequencies (percentages).
ADPKD: Autosomal dominant polycystic kidney disease; CCB: Calcium channel blocker; CKD: Chronic kidney disease; RAS: Renin angiotensin system.

There were no significant differences in antihypertensive prescription patterns over the 12-mo and 24-mo follow-up period (Tables 6 and 7). Overall, there were more patients achieving BP < 140/90 mmHg at 12 mo (52% *vs* 48%, *P* = 0.008) and at 24 mo (51.7% *vs* 48%, *P* = 0.015) compared to baseline. However, when only patients on three or more agents over the 24-mo follow-up period were considered, there were no statistically significant results as to whether more patients achieved BP < 140/90 mmHg (Tables 8 and 9).

Table 4 Number of patients prescribed with each antihypertensive class at baseline, organized by urine albumin-creatinine ratio categories at baseline

Antihypertensive class	uACR < 30, *n* = 1355[1,2]	uACR 30-300, *n* = 1236[1,2]	uACR > 300, *n* = 248[1,2]	Total, *n* = 2839[1,3]	*P* value[1]
None	148 (10.9)	112 (9.1)	12 (4.8)	272 (9.6)	< 0.001
Three or more agents	547 (40.4)	530 (42.9)	155 (62.5)	1232 (43.4)	< 0.001
Diuretic (thiazide and loop)	656 (48.4)	542 (43.9)	148 (59.7)	1346 (47.4)	< 0.001
CCB (dihydropyridine)	477 (35.2)	516 (41.7)	122 (49.2)	1115 (39.3)	< 0.001
CCB (non- dihydropyridine)	61 (4.5)	54 (4.4)	11 (4.4)	126 (4.4)	0.987
Beta-blocker	458 (33.8)	418 (33.8)	93 (37.5)	969 (34.1)	0.504
Alpha blocker	265 (19.6)	335 (27.1)	87 (35.1)	687 (24.2)	< 0.001
Central agent	45 (3.3)	69 (5.6)	23 (9.3)	137 (4.8)	< 0.001
Vasodilator	11 (0.8)	16 (1.3)	1 (0.4)	28 (1.0)	0.288
RAS blocker	840 (62.0)	753 (61.0)	174 (70.2)	1767 (62.2)	0.023
Dual RAS blockers	49 (3.6)	80 (6.5)	41 (16.5)	170 (6.0)	< 0.001
Spironolactone/eplerenone	52 (3.8)	29 (2.3)	11 (4.4)	92 (3.2)	0.054

[1]Absolute number for frequencies (percentages). The *P* values were calculated by the χ^2 test.
[2]uACR in mg/mg = -0.171 + 0.780 urine protein-creatinine ratio in mg/mg.
[3]Total was 2839 rather than 3230 as in previous tables as some patients were missing uACR data.
CCB: Calcium channel blocker; RAS: Renin angiotensin system; uACR: Urine albumin-creatinine ratio in mg/g.

Table 5 Number of patients prescribed with each antihypertensive class at baseline, organized by categories according to the prevalence of congestive cardiac failure and other cardiovascular events at baseline

Antihypertensive class	CCF, *n* = 556[1]	No CCF, *n* = 2674[1]	*P* value[1]	CVE, *n* = 1829[1]	No CVE, *n* = 1401[1]	*P* value[1]
None	22 (4.0)	306 (11.4)	< 0.001	72 (5.1)	256 (14.0)	< 0.001
Diuretic (thiazide and loop)	381 (68.4)	1144 (42.8)	< 0.001	818 (58.4)	707 (38.7)	< 0.001
CCB (dihydropyridine)	192 (34.5)	1064 (39.8)	0.021	561 (40.0)	695 (38.0)	0.238
CCB (non-dihydropyridine)	32 (5.8)	102 (3.8)	0.037	92 (6.6)	42 (2.3)	< 0.001
Beta blocker	248 (44.6)	859 (32.1)	< 0.001	621 (44.3)	486 (26.6)	< 0.001
Alpha blocker	140 (25.2)	639 (23.9)	0.520	385 (27.5)	394 (21.7)	< 0.001
Central agent	29 (5.2)	121 (4.5)	0.481	73 (5.2)	77 (4.2)	0.180
Vasodilator	4 (0.7)	26 (1.0)	0.572	17 (1.2)	13 (0.7)	0.140
RAS blocker	360 (64.7)	1623 (60.7)	0.074	839 (42.3)	1144 (57.7)	0.124
Dual RAS blockers	24 (4.3)	163 (6.1)	0.102	70 (37.4)	117 (62.6)	0.091
Spironolactone/eplerenone	56 (10.1)	56 (2.1)	< 0.001	80 (5.7)	32 (1.7)	< 0.001

[1]Absolute number for frequencies (percentages). The *P* values were calculated by the χ^2 test.
CCB: Calcium channel blocker; CCF: Congestive cardiac failure; CVE: Cardiovascular events; RAS: Renin angiotensin system.

Associations between antihypertensive prescription patterns and clinical outcomes

In Cox regression models, the prescription of three or more antihypertensive agents was strongly associated with all-cause mortality (multivariate model 3: hazard ratio: 1.14; 95% confidence interval: 1.03-1.26, $P = 0.008$) (Table 10). A similar association was observed when the outcome considered was progression to ESKD (multivariate model 3: hazard ratio: 1.47; 95% confidence interval: 1.25-1.72, $P < 0.001$) (Table 11).

Kaplan-Meier analysis illustrated significant differences in survival outcomes (all-cause mortality and RRT-free survival) between patients receiving three or more compared to those with less than three antihypertensive agents prescribed (log-rank, $P < 0.001$) (Figures 1 and 2). Being on RAS blockers was associated with a higher survival (log-rank, $P < 0.001$) but demonstrated no differences in terms of reaching ESKD and requiring RRT (log-rank, $P = 0.113$) (Figures 3 and 4).

Table 6 Number of patients prescribed with each antihypertensive class at baseline and at the 12-mo follow-up

Antihypertensive class	Baseline, *n* = 2256[1]	12-mo follow-up, *n* = 2256[1]	*P* value[1]
Diuretic (thiazide and loop)	1131 (50.1)	1107 (49.1)	0.475
CCB (dihydropyridine)	905 (40.1)	930 (41.2)	0.449
CCB (non- dihydropyridine)	102 (4.5)	90 (4.0)	0.376
Beta blocker	783 (34.7)	767 (34.0)	0.616
Alpha blocker	544 (24.1)	558 (24.7)	0.628
Central agent	111 (4.9)	117 (5.2)	0.683
Vasodilator	19 (0.8)	15 (0.7)	0.491
RAS blocker	1416 (62.8)	1383 (61.3)	0.311
Dual RAS blockers	145 (6.4)	163 (7.2)	0.288
Spironolactone/eplerenone	84 (3.7)	73 (3.2)	0.372

[1]Absolute number for frequencies (percentages). The *P* values were calculated by the χ^2 test.
CCB: Calcium channel blocker, RAS: Renin angiotensin system.

Table 7 Number of patients prescribed with each antihypertensive class at baseline and the 12-mo and 24-mo follow-ups

Antihypertensive class	Baseline, *n* = 1708[1]	12-mo follow-up, *n* = 1708[1]	24-mo follow-up, *n* = 1708[1]	*P* value[1]
Diuretic (thiazide and loop)	895 (52.4)	874 (51.2)	839 (49.1)	0.153
CCB (dihydropyridine)	696 (40.7)	710 (41.6)	646 (37.8)	0.063
CCB (non- dihydropyridine)	83 (4.9)	74 (4.3)	75 (4.4)	0.719
Beta blocker	588 (34.4)	581 (34.0)	560 (32.8)	0.573
Alpha blocker	421 (24.6)	433 (25.4)	394 (23.1)	0.281
Central agent	81 (4.7)	90 (5.3)	66 (5.0)	0.779
Vasodilator	18 (1.1)	14 (0.8)	18 (1.1)	0.724
RAS blocker	1076 (63.0)	1077 (63.1)	1056 (61.8)	0.417
Dual RAS blockers	99 (5.8)	127 (7.4)	122 (7.1)	0.127
Spironolactone/eplerenone	58 (3.4)	49 (2.9)	43 (2.5)	0.309

[1]Absolute number for frequencies (percentages). The *P* values were calculated by the χ^2 test.
CCB: Calcium channel blocker, RAS: Renin angiotensin system.

Table 8 Patient proportion achieving blood pressure < 140/90 mmHg at the 12-mo and 24-mo follow-ups in comparison to baseline

Time	Total number of patients	Number of patients with BP < 140/90 mmHg[1]	*P* value[1]
Baseline	3230	1549 (48.0)	-
12-mo follow-up	2096	1083 (52.0)	0.008
24-mo follow-up	1541	797 (51.7)	0.015

[1]Absolute number for frequency (percentage). The *P* values were calculated by the χ^2 test.
BP: Blood pressure.

Linear regression analysis concluded that the annual rate of decline in eGFR was significantly higher in patients receiving three or more antihypertensive agents (-1.79 *vs* -1.07 mL/min/1.73 m²/year, $P < 0.001$) compared to those receiving less (Table 12).

Table 9 Patient proportion achieving blood pressure < 140/90 mmHg at the 12-mo and 24-mo follow-ups in comparison to baseline (patients on three or more antihypertensive agents)

	Total number of patients on three or more agents	Number of patients with BP < 140/90 mmHg[1]	*P* value[1]
Baseline	1383	629 (45.5)	-
12-mo follow-up	961	473 (49.2)	0.074
24-mo follow-up	724	359 (49.6)	0.072

[1]Absolute number for frequency (percentage). The *P* values were calculated by the χ^2 test.
BP: Blood pressure.

Table 10 Cox regression analysis demonstrating associations between the prescription of three or more antihypertensive agents with all-cause mortality

Analysis	HR (95%CI)[1]	*P* value[1]
Univariate model	1.55 (1.41-1.69)	< 0.001
Multivariate model 1[2]	1.33 (1.21-1.45)	< 0.001
Multivariate model 2[3]	1.23 (1.12-1.35)	< 0.001
Multivariate model 3[4]	1.15 (1.04-1.27)	0.006

[1]Absolute number for hazard ratio alongside corresponding 95% confidence interval and *P* value.
[2]Multivariate model 1: adjusted for age, sex, ethnicity, smoking status, and alcohol intake.
[3]Multivariate model 2: adjusted for all covariates of model 1 plus diabetes, any cardiovascular disease (ischemic heart disease or myocardial infarction or congestive cardiac failure or cerebrovascular accident or peripheral vascular disease), and blood pressure control < 140/90 mmHg.
[4]Multivariate model 3: adjusted for all covariates of model 2 plus estimated glomerular filtration rate and urine albumin-creatinine ratio.
HR: Hazard ratio; 95%CI: 95% confidence interval.

Table 11 Cox regression analysis demonstrated associations between the prescription of three or more antihypertensive agents with progression to end stage kidney disease

Analysis	HR (95%CI)[1]	*P* value[1]
Univariate model	1.60 (1.39-1.84)	< 0.001
Multivariate model 1[2]	1.81 (1.56-2.10)	< 0.001
Multivariate model 2[3]	1.55 (1.37-1.76)	< 0.001
Multivariate model 3[4]	1.31 (1.14-1.50)	< 0.001

[1]Absolute number for hazard ratio alongside corresponding 95% confidence interval and *P* value.
[2]Multivariate model 1: adjusted for age, sex, ethnicity, smoking status, and alcohol intake.
[3]Multivariate model 2: adjusted for all covariates of model 1 plus diabetes, any cardiovascular disease (ischemic heart disease or myocardial infarction or congestive cardiac failure or cerebrovascular accident or peripheral vascular disease), and blood pressure control < 140/90 mmHg.
[4]Multivariate model 3: adjusted for all covariates of model 2 plus estimated glomerular filtration rate and urine albumin-creatinine ratio.
HR: Hazard ratio; 95%CI: 95% confidence interval

DISCUSSION

In this study, we evaluated antihypertensive prescription patterns in patients from the SKS-CKD database, corresponding this to baseline eGFR, uACR, primary kidney disease aetiology and the presence of cardiovascular morbidities, and monitored prescription patterns over a 24-mo follow-up period. The number of antihypertensive agents prescribed for each patient was correlated with clinical outcomes, namely all-cause mortality and progression to ESKD.

Across the SKS-CKD cohort at baseline, RAS blockers were the most commonly prescribed agents for management of hypertension, followed by diuretics, dihydropyridine CCBs, and beta blockers. RAS blocker prescriptions decreased in patients with CKD stage 5 at baseline, whereas diuretics, dihydropyridine CCBs, and beta blockers were prescribed more frequently for patients with lower eGFR. Surprisingly, although it has not been widely advocated for use as an antihypertensive in current guidelines, alpha blockers were amongst the more commonly prescribed antihypertensive agents

Table 12 Rate of decline in estimated glomerular filtration rate in patients with three or more antihypertensive agents *vs* less than three antihypertensive agents prescribed

eGFR	Three or more agents prescribed[1]	Less than three agents prescribed[1]	*P* value[1]
[2]Delta eGFR, mL/min/1.73 m^2/yr	-1.79 (-4.25 to -0.07)	-1.07 (-3.10 to 0.72)	< 0.001

[1]Expressed as a median (interquartile range). The *P* value was calculated by the Mann-Whitney *U* test.
[2]Delta estimated glomerular filtration rate analysis included 3068 patients with estimated glomerular filtration rate data available as defined.
eGFR: Estimated glomerular filtration rate.

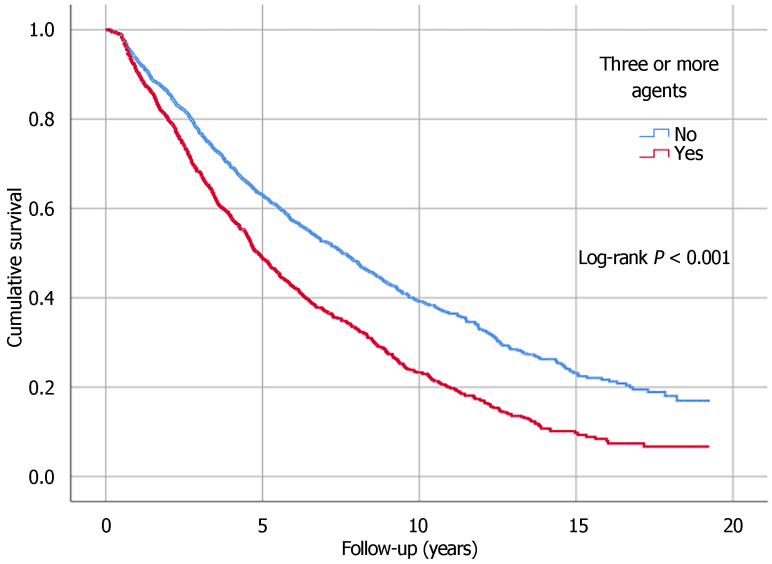

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Figure 1 Kaplan-Meier analysis demonstrated associations between the prescription of three or more antihypertensive agents and all-cause mortality (log-rank, *P* < 0.001).

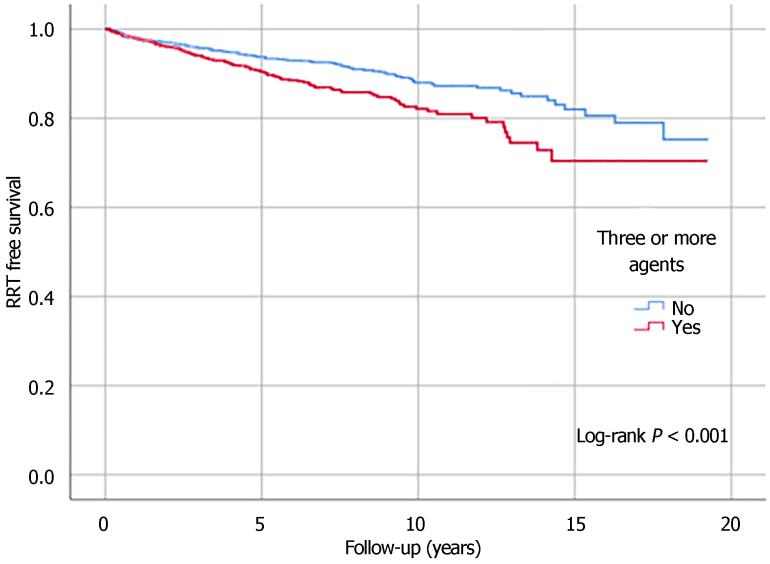

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Figure 2 Kaplan-Meier analysis demonstrated associations between the prescription of three or more antihypertensive agents and renal replacement therapy free survival (log-rank, *P* < 0.001). RRT: Renal replacement therapy.

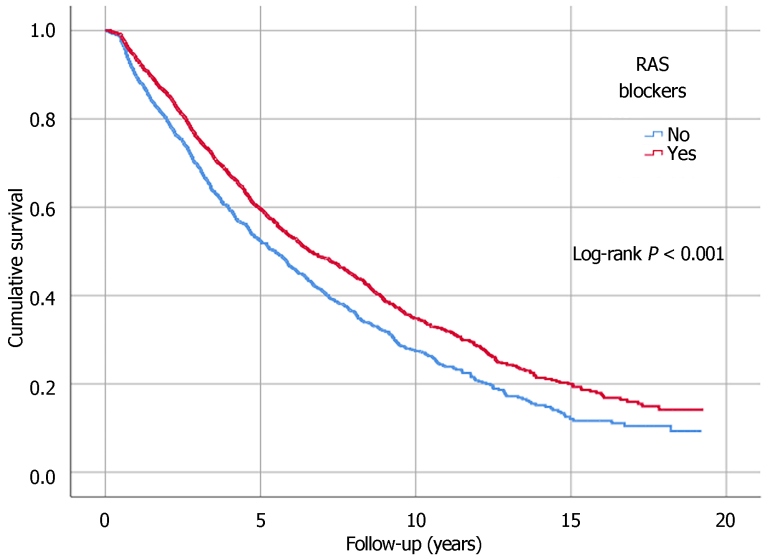

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Figure 3 Kaplan-Meier analysis demonstrated associations between being prescribed renin angiotensin system blocker at baseline and all-cause mortality (log-rank, *P* < 0.001). RAS: Renin angiotensin system.

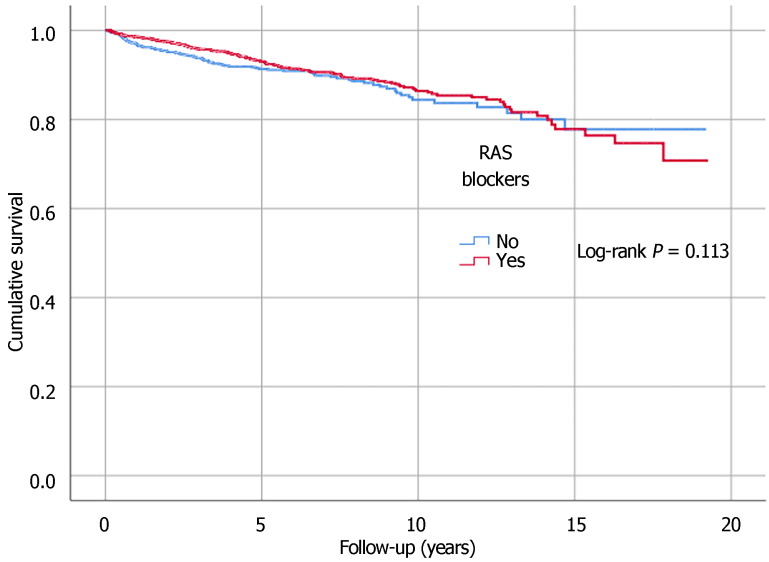

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Figure 4 Kaplan-Meier analysis demonstrated associations between being prescribed renin angiotensin system blocker at baseline and renal replacement therapy free survival (log-rank, *P* = 0.136). RAS: Renin angiotensin system.

amongst patients in SKS-CKD, especially for those in the lower eGFR ranges. A major adverse effect of alpha blockers is orthostatic hypotension in patients with kidney function impairment[20-22]. The purposes of prescribing alpha blockers may not be solely for lowering of BP, as a substantial proportion of patients with benign prostatic hyperplasia are routinely initiated on them to relieve symptoms and improve urinary flow[23].

RAS blockers, diuretics, and dihydropyridine CCBs were prescribed with increasing frequency in patients with a greater degree of uACR. Ultimately, with an increase in the uACR category, a greater proportion of patients were prescribed more antihypertensive agents. RAS blockers remain the primary antihypertensive agents prescribed for patients with all forms of primary kidney disease. For CKD patients with CCF, the prescriptions of diuretics, beta blockers, and potassium sparing diuretics (spironolactone and eplerenone) were significantly higher compared to those without. This pattern was similar when comparing antihypertensive prescribing patterns between CKD patients with pre-existing cardiovascular events and those without.

Our analysis demonstrated that antihypertensive prescribing patterns at 12 mo and 24 mo had only minimally changed compared to baseline, but this was most likely because most patients had been enrolled in the renal service well before entry into the SKS. When determining associations between the number of antihypertensive agents prescribed and clinical outcomes, patients receiving a higher number of antihypertensive agents had worsened outcomes, namely

increased all-cause mortality and reaching ESKD. Such associations remained following adjustment of baseline demographic factors (*i.e.* age, sex, ethnicity, smoking status, and alcohol intake), plus diabetes, cardiovascular comorbidities, baseline eGFR, and uACR.

Consensus recommendation to commence ACEI or angiotensin receptor ARB as a first-line antihypertensive treatment option for CKD patients, particularly for those with proteinuria and/or reduced eGFR defined by eGFR < 60 mL/min/1.73 m^2 has been reached across the major international societies in cardiology and nephrology such as the American College of Cardiology, the American Heart Association, and KDIGO[8,24]. The updated 2021 KDIGO clinical practice guideline for BP management in CKD continues to advocate this approach in patients with hypertension and CKD, with or without diabetes, and not receiving dialysis[24]. Where an adult patient has a transplanted kidney, commencing an ARB or dihydropyridine CCB has been recommended[24]. In the United Kingdom, the National Institute of Health and Care Excellence (NICE) guideline defines BP targets (clinic measured) for patients with CKD according to the patient's uACR[25]. Adult CKD patients are divided into 2 groups: those with a uACR < 70 mg/mmol (618.8 mg/g); and those with a uACR > 70 mg/mmol (618.8 mg/g). In patients with a uACR < 70 mg/mmol (618.8 mg/g), the BP target is below 140/90 mmHg, whereas in patients with a uACR > 70 mg/mmol (618.8 mg/g), the BP target is below 130/80 mmHg.

An ACEI or ARB is first-line treatment for hypertension in CKD patients with uACR > 30mg/mmol (265.2 mg/g). A thiazide diuretic or CCB is to be used as second-line medications. While both dihydropyridine CCB and non-dihydropyridine CCB have been shown to have similar effects in terms of BP control, non-dihydropyridine CCBs such as verapamil and diltiazem have been shown to reduce proteinuria to a greater extent. However, prescribing non-dihydropyridine CCBs over dihydropyridine CCBs would generally appear to be less popular in actual clinical practice, mainly due to concerns of increased risk of cardiac adverse effects such as bradycardia that could be potentially life-threatening in severe cases[26]. A potassium sparing agent such as spironolactone can also be added, but due to the increased risk of hyperkalaemia, this is recommended only if there is persistent poor BP control following the addition of a thiazide diuretic. Whilst these are the main antihypertensive options as per NICE guidelines, other antihypertensive classes exist, such as alpha blockers, direct renin inhibitors, vasodilators, and centrally acting antihypertensive agents. These medications are not currently recommended under the NICE and other international guidelines for various reasons, such as the presence of adverse effects as well as the lack of evidence that they offer a strong clinical benefit for CKD patients with hypertension.

A number of studies have been conducted reviewing antihypertensive prescribing patterns in patients with CKD. Amongst the more recent studies that have followed the introduction of updated hypertension guidelines, a study conducted by Magvanjav *et al*[12] utilized electronic health record data from 5658 CKD patients with hypertension to examine their antihypertensive drug prescribing patterns, BP control, and risk factors for resistant hypertension. As found in our study and in observational data stated from recent hypertension guidelines, Magvanjav *et al*[12] noted that 64% of patients were prescribed an ACEI or ARB. They also concluded that BP was better controlled in patients who were prescribed a combination of medications that included a diuretic and beta blocker. Another study by Alencar de Pinho *et al*[13] compared antihypertensive prescribing patterns in CKD patients internationally and similarly found that ACEI or ARB was the most commonly prescribed antihypertensive class. However, the investigators noted significant variations in antihypertensive medication prescribing practices globally for all antihypertensive agents across different stages of CKD. Taking ACEI or ARB for example, Alencar de Pinho *et al*[13] observed that the prevalence of an ACEI or ARB prescription varied between 54% and 91% across different countries. This emphasizes that significant variations remain regarding clinicians' approaches to antihypertensive treatment prescription for their CKD patients within the real-world setting, whether they follow a guideline-recommended algorithm or basing their approach from personal clinical experiences and preferences.

Indeed there are numerous patient-specific and clinical challenges when treating hypertension in CKD, of which clinician variation in antihypertensive prescription practices is only one issue. This conundrum may be explained by the variability in national and international guideline recommendations at present. Areas where a global consensus has not been reached are the BP thresholds that determine when treatment initiation is indicated, for instance. There also remains no unified agreement on the BP targets to be achieved amongst CKD patients. More importantly, there is continuous debate and discussion on how best to optimize antihypertensive therapy for BP control and cardiorenal protection. These are avenues of research where further work is required.

There is now an increased indication for adding sodium glucose cotransport (SGLT2) inhibitors to the current portfolio of recommended medications for hypertension management in CKD, given their emergence as a therapeutic option for cardiorenal protection in people with and without diabetes[27]. Large, randomized, placebo-controlled trials have pointed to the potential of SGLT2 inhibitors as having positive effects on BP control in both office and out-of-office contexts. The SACRA, EMPA-REG BP, and CREDENCE trials were amongst the clinical trials that have made these conclusions[28-30]. The post hoc analysis of the CREDENCE trial demonstrated the BP-lowering effect of canagliflozin for patients with resistant hypertension, which is novel and encouraging[29]. Additional studies are needed to validate the role of SGLT2 inhibitors in optimizing BP control and reducing adverse cardiovascular outcomes amongst patients living with CKD and hypertension, particularly those with resistant hypertension.

Despite the main strength of our study being inclusion of an ethnically and socioeconomically diverse CKD patient group, as well as being conducted over a 20-year period, there are limitations to acknowledge. One limitation was an inability to clearly correlate details relating to the indication(s) for antihypertensive medication prescription and any adjustments during the follow-up period due to multiple clinicians being involved in a patient's management. Furthermore, it is unclear if diuretics were prescribed as an antihypertensive agent within this context, or intended for other clinical purposes (*e.g.*, for peripheral oedema). Understanding the indications for prescription of particular antihypertensive medication(s) would have been useful in determining the true patterns of antihypertensive prescribing practices in this study. Also, as our centre does not complete urinary antihypertensive screens routinely, there is always

the confounding impact of drug non-compliance amongst patients receiving three or more antihypertensive agents. This contributes to poor BP control and its associated morbidity and mortality outcomes. Finally, there was incomplete data on determining the rate of decline in eGFR when comparing between CKD patients with three or more antihypertensive agents *vs* less than three antihypertensive agents prescribed due to delta eGFR data being unavailable for 162 patients (5% of entire cohort).

CONCLUSION

In summary, RAS blockers were found to be the most commonly prescribed antihypertensive agents, followed by diuretics and CCBs, which are recommended as second-line antihypertensive treatment options. Diuretics, beta blockers, and mineralocorticoid antagonists were found to be more commonly prescribed in CKD patients with cardiovascular comorbidities. Whilst our study results aligned with that of expectations from the current NICE guideline algorithm, further work determining optimal strategies in approaching antihypertensive prescription for CKD patients at both an individual and policy level is needed to reduce the variations currently observed in clinical practice. The opportunity to introduce newer and potentially more cost-effective therapies in the form of SGLT2 inhibitors for hypertension management in CKD is attractive and could be revolutionary in addressing these challenges, and continued research in this area is anticipated.

ARTICLE HIGHLIGHTS

Research background

Hypertension is a major contributor towards the progression of chronic kidney disease (CKD) and a leading consequence of CKD. Despite standard guidelines, clinician practices on managing hypertension in CKD patients remain variable.

Research motivation

It is important to explore the factors relating to CKD patients that influences a clinician's decision to use specific antihypertensive agents with the aim to better standardize current antihypertensive prescription practices.

Research objectives

To investigate hypertension management practices in CKD patients within a real-world setting.

Research methods

We retrospectively analysed patients recruited into the Salford Kidney Study database. Data including patient demographic information, comorbidities, and a detailed antihypertensive medication history were reviewed. Prescription patterns of antihypertensive agents were explored based on estimated glomerular filtration rate expressed as mL/min/1.73 m^2, urine albumin-creatinine ratio, primary kidney disease aetiology, and cardiovascular disease. The association between being prescribed three or more antihypertensive agents and clinical outcomes (*i.e.* all-cause mortality and reaching end stage kidney disease) was also studied.

Research results

A total of 3230 non-dialysis dependent CKD patients with data collected between October 2002 and December 2019 were included. The most frequently prescribed antihypertensive agents were renin angiotensin system blockers (61%), followed by diuretics (47%), dihydropyridine calcium channel blockers (39%), and beta blockers (34%). A greater proportion of patients were taking three or more antihypertensive agents with advancing CKD stages (53% of CKD stage 5 patients *vs* 26% of CKD stage 2 patients) and as the urine albumin-creatinine ratio increased (category A3: 62% *vs* category A1: 40%, $P < 0.001$). The prescription of three or more antihypertensive agents was associated with all-cause mortality, independent of blood pressure control (hazard ratio: 1.15; 95% confidence interval: 1.04-1.27, $P = 0.006$).

Research conclusions

Renin angiotensin system blockers were found to be the most prescribed antihypertensive agents, followed by diuretics and calcium channel blockers. Outcomes were poorer in CKD patients with poor blood pressure control despite being on multiple antihypertensive agents.

Research perspectives

Our study results aligned with expectations from the current National Institute of Health and Care Excellence guideline algorithm; further work determining optimal strategies in approaching antihypertensive prescriptions for CKD patients at both an individual and policy level is needed to reduce the variations currently observed in clinical practice.

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FOOTNOTES

Author contributions: Chinnadurai R drafted the manuscript, led the design and oversight of the study, led the data analysis, and participated in drafting and revising the manuscript; Wu HHL drafted the manuscript and participated in revising the manuscript; Abuomar J participated in the design of the study and led data collection; Rengarajan S participated in the design of the study and assisted in data collection; New D participated in revising the manuscript; Green D participated in revising the manuscript; Kalra PA supervised the design and oversight of the study and participated in revising the manuscript; All authors read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the institutional review board of the North West - Greater Manchester South Research Ethics Committee in the United Kingdom.

Informed consent statement: All study participants, or their legal guardian, provided written consent prior to study enrolment.

Conflict-of-interest statement: The authors of this manuscript declare that they have no conflicts of interest to disclose in relation to the contents of this study.

Data sharing statement: There are no additional data available.

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REFERENCES

1 **Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group**. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; **3**: 1-50
2 **Foreman KJ**, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, Pletcher MA, Smith AE, Tang K, Yuan CW, Brown JC, Friedman J, He J, Heuton KR, Holmberg M, Patel DJ, Reidy P, Carter A, Cercy K, Chapin A, Douwes-Schultz D, Frank T, Goettsch F, Liu PY, Nandakumar V, Reitsma MB, Reuter V, Sadat N, Sorensen RJD, Srinivasan V, Updike RL, York H, Lopez AD, Lozano R, Lim SS, Mokdad AH, Vollset SE, Murray CJL. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet* 2018; **392**: 2052-2090 [PMID: 30340847 DOI: 10.1016/S0140-6736(18)31694-5]
3 **Ku E**, Johansen KL, McCulloch CE. Time-Centered Approach to Understanding Risk Factors for the Progression of CKD. *Clin J Am Soc Nephrol* 2018; **13**: 693-701 [PMID: 29602779 DOI: 10.2215/CJN.10360917]
4 **Kalantar-Zadeh K**, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. *Lancet* 2021; **398**: 786-802 [PMID: 34175022 DOI: 10.1016/S0140-6736(21)00519-5]
5 **Anders HJ**, Huber TB, Isermann B, Schiffer M. CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. *Nat Rev Nephrol* 2018; **14**: 361-377 [PMID: 29654297 DOI: 10.1038/s41581-018-0001-y]
6 **Ku E**, Lee BJ, Wei J, Weir MR. Hypertension in CKD: Core Curriculum 2019. *Am J Kidney Dis* 2019; **74**: 120-131 [PMID: 30898362 DOI: 10.1053/j.ajkd.2018.12.044]
7 **Muntner P**, Anderson A, Charleston J, Chen Z, Ford V, Makos G, O'Connor A, Perumal K, Rahman M, Steigerwalt S, Teal V, Townsend R, Weir M, Wright JT Jr; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis* 2010; **55**: 441-451 [PMID: 19962808 DOI: 10.1053/j.ajkd.2009.09.014]
8 **Whelton PK**, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD,

Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018; **71**: 1269-1324 [PMID: 29133354 DOI: 10.1161/HYP.0000000000000066]

9 **Lv J**, Ehteshami P, Sarnak MJ, Tighiouart H, Jun M, Ninomiya T, Foote C, Rodgers A, Zhang H, Wang H, Strippoli GF, Perkovic V. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. *CMAJ* 2013; **185**: 949-957 [PMID: 23798459 DOI: 10.1503/cmaj.121468]

10 **Pugh D**, Gallacher PJ, Dhaun N. Management of Hypertension in Chronic Kidney Disease. *Drugs* 2019; **79**: 365-379 [PMID: 30758803 DOI: 10.1007/s40265-019-1064-1]

11 **Fraser SD**, Roderick PJ, McIntyre NJ, Harris S, McIntyre CW, Fluck RJ, Taal MW. Suboptimal blood pressure control in chronic kidney disease stage 3: baseline data from a cohort study in primary care. *BMC Fam Pract* 2013; **14**: 88 [PMID: 23800117 DOI: 10.1186/1471-2296-14-88]

12 **Magvanjav O**, Cooper-DeHoff RM, McDonough CW, Gong Y, Segal MS, Hogan WR, Johnson JA. Antihypertensive therapy prescribing patterns and correlates of blood pressure control among hypertensive patients with chronic kidney disease. *J Clin Hypertens (Greenwich)* 2019; **21**: 91-101 [PMID: 30427124 DOI: 10.1111/jch.13429]

13 **Alencar de Pinho N**, Levin A, Fukagawa M, Hoy WE, Pecoits-Filho R, Reichel H, Robinson B, Kitiyakara C, Wang J, Eckardt KU, Jha V, Oh KH, Sola L, Eder S, de Borst M, Taal M, Feldman HI, Stengel B; International Network of Chronic Kidney Disease cohort studies (iNET-CKD). Considerable international variation exists in blood pressure control and antihypertensive prescription patterns in chronic kidney disease. *Kidney Int* 2019; **96**: 983-994 [PMID: 31358344 DOI: 10.1016/j.kint.2019.04.032]

14 **Imaizumi T**, Hamano T, Fujii N, Huang J, Xie D, Ricardo AC, He J, Soliman EZ, Kusek JW, Nessel L, Yang W, Maruyama S, Fukagawa M, Feldman HI; CRIC Study Investigators. Cardiovascular disease history and β-blocker prescription patterns among Japanese and American patients with CKD: a cross-sectional study of the CRIC and CKD-JAC studies. *Hypertens Res* 2021; **44**: 700-710 [PMID: 33479519 DOI: 10.1038/s41440-020-00608-8]

15 **Prasad N**, Yadav AK, Kundu M, Sethi J, Jaryal A, Sircar D, Modi GK, Kamboj K, Sahay M, Gopalakrishnan N, Kaur P, Vikrant S, Varughese S, Baid-Agrawal S, Singh S, Gang S, Parameswaran S, Kumar V, Ghosh A, Jha V. Prescription Practices in Patients With Mild to Moderate CKD in India. *Kidney Int Rep* 2021; **6**: 2455-2462 [PMID: 34514206 DOI: 10.1016/j.ekir.2021.06.011]

16 **Thomas R**, Sam S, Neelaphar P, Shabeeb P, Vishwanath BA. A study on prescribing pattern of antihypertensive in chronic kidney disease patients. *J Drug Deliv Ther* 2020; **10**: 75-81 [DOI: 10.22270/jddt.v10i3-s.4139]

17 **Raman M**, Green D, Middleton RJ, Kalra PA. Comparing the impact of older age on outcome in chronic kidney disease of different etiologies: a prospective cohort study. *J Nephrol* 2018; **31**: 931-939 [PMID: 30187380 DOI: 10.1007/s40620-018-0529-8]

18 **Ali I**, Chinnadurai R, Ibrahim ST, Kalra PA. Adverse outcomes associated with rapid linear and non-linear patterns of chronic kidney disease progression. *BMC Nephrol* 2021; **22**: 82 [PMID: 33676423 DOI: 10.1186/s12882-021-02282-5]

19 **Mertens B**, Verhofstede S, Abramowicz D, Couttenye MM. A surprising journey into the conversion of urinary protein creatinine ratio to urinary albumin creatinine ratio as needed in the Kidney Failure Risk Equation. *Clin Kidney J* 2021; **14**: 1481-1482 [PMID: 33959276 DOI: 10.1093/ckj/sfaa201]

20 **Hundemer GL**, Knoll GA, Petrcich W, Hiremath S, Ruzicka M, Burns KD, Edwards C, Bugeja A, Rhodes E, Sood MM. Kidney, Cardiac, and Safety Outcomes Associated With α-Blockers in Patients With CKD: A Population-Based Cohort Study. *Am J Kidney Dis* 2021; **77**: 178-189.e1 [PMID: 32920153 DOI: 10.1053/j.ajkd.2020.07.018]

21 **Aytaş G**, Kazancıoğlu R, Elçioğlu ÖC, Gürsu M, Artan AS, Yabacı A, Soysal P, Bilgi K, Özçelik S. Comparative Evaluation of Orthostatic Hypotension in Patients with Diabetic Nephropathy. *Kidney Blood Press Res* 2021; **46**: 574-580 [PMID: 34284392 DOI: 10.1159/000517316]

22 **Biaggioni I**. Orthostatic Hypotension in the Hypertensive Patient. *Am J Hypertens* 2018; **31**: 1255-1259 [PMID: 29982276 DOI: 10.1093/ajh/hpy089]

23 **Lepor H**. Alpha blockers for the treatment of benign prostatic hyperplasia. *Rev Urol* 2007; **9**: 181-190 [PMID: 18231614]

24 **Cheung AK**, Chang TI, Cushman WC, Furth SL, Hou FF, Ix JH, Knoll GA, Muntner P, Pecoits-Filho R, Sarnak MJ, Tobe SW, Tomson CRV, Lytvyn L, Craig JC, Tunnicliffe DJ, Howell M, Tonelli M, Cheung M, Earley A, Mann JFE. Executive summary of the KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int* 2021; **99**: 559-569 [PMID: 33637203 DOI: 10.1016/j.kint.2020.10.026]

25 **National Institute of Clinical Excellence**. Chronic kidney disease: assessment and management. Nov 24, 2021. [Cited 30 June 2023]. Available from: https://www.nice.org.uk/guidance/ng203

26 **Buckley N**, Dawson A, Whyte I. Calcium channel blockers. *Medicine* 2007; **35**: 599-602 [DOI: 10.1016/j.mpmed.2007.08.025]

27 **Kario K**, Ferdinand KC, Vongpatanasin W. Are SGLT2 Inhibitors New Hypertension Drugs? *Circulation* 2021; **143**: 1750-1753 [PMID: 33939525 DOI: 10.1161/CIRCULATIONAHA.121.053709]

28 **Kario K**, Okada K, Kato M, Nishizawa M, Yoshida T, Asano T, Uchiyama K, Niijima Y, Katsuya T, Urata H, Osuga JI, Fujiwara T, Yamazaki S, Tomitani N, Kanegae H. Twenty-Four-Hour Blood Pressure-Lowering Effect of a Sodium-Glucose Cotransporter 2 Inhibitor in Patients With Diabetes and Uncontrolled Nocturnal Hypertension: Results From the Randomized, Placebo-Controlled SACRA Study. *Circulation* 2019; **139**: 2089-2097 [PMID: 30586745 DOI: 10.1161/CIRCULATIONAHA.118.037076]

29 **Tikkanen I**, Narko K, Zeller C, Green A, Salsali A, Broedl UC, Woerle HJ; EMPA-REG BP Investigators. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. *Diabetes Care* 2015; **38**: 420-428 [PMID: 25271206 DOI: 10.2337/dc14-1096]

30 **Ye N**, Jardine MJ, Oshima M, Hockham C, Heerspink HJL, Agarwal R, Bakris G, Schutte AE, Arnott C, Chang TI, Górriz JL, Cannon CP, Charytan DM, de Zeeuw D, Levin A, Mahaffey KW, Neal B, Pollock C, Wheeler DC, Luca Di Tanna G, Cheng H, Perkovic V, Neuen BL. Blood Pressure Effects of Canagliflozin and Clinical Outcomes in Type 2 Diabetes and Chronic Kidney Disease: Insights From the CREDENCE Trial. *Circulation* 2021; **143**: 1735-1749 [PMID: 33554616 DOI: 10.1161/CIRCULATIONAHA.120.048740]

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SYSTEMATIC REVIEWS

Heterogeneity in cardiorenal protection by Sodium glucose cotransporter 2 inhibitors in heart failure across the ejection fraction strata: Systematic review and meta-analysis

Saeed Taheri

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Abstract

BACKGROUND

Gliflozins or Sodium glucose cotransporter 2 inhibitors (SGLT2i) are relatively novel antidiabetic medications that have recently been shown to represent favorable effects on patients' cardiorenal outcomes. However, there is shortage of data on potential disparities in this therapeutic effect across different patient subpopulations.

AIM

To investigate differential effects of SGLT2i on the cardiorenal outcomes of heart failure patients across left ventricular ejection fraction (LVEF) levels.

METHODS

Literature was searched systematically for the large randomized double-blind controlled trials with long enough follow up periods reporting cardiovascular and renal outcomes in their patients regarding heart failure status and LVEF levels. Data were then meta-analyzed after stratification of the pooled data across the LVEF strata and New York Heart Associations (NYHA) classifications for heart failure using Stata software version 17.0.

RESULTS

The literature search returned 13 Large clinical trials and 13 *post hoc* analysis reports. Meta-analysis of the effects of gliflozins on the primary composite outcome showed no significant difference in efficacy across the heart failure subtypes, but higher efficacy were detected in patient groups at lower NYHA classifications (I^2 = 46%, P = 0.02). Meta-analyses across the LVEF stratums revealed that a baseline LVEF lower than 30% was associated with enhanced improvement in the primary composite outcome compared to patients with higher LVEF levels at the borderline statistical significance (HR: 0.70, 95%CI: 0.60 to 0.79 *vs* 0.81, 95%CI: 0.75 to 0.87; respectively, P = 0.06). Composite renal

outcome was improved significantly higher in patients with no heart failure than in heart failure patients with preserved ejection fraction (HFpEF) (HR: 0.60, 95%CI: 0.49 to 0.72 *vs* 0.94, 95%CI: 0.74 to 1.13; *P* = 0.04). Acute renal injury occurred significantly less frequently in heart failure patients with reduced ejection fraction who received gliflozins than in HFpEF (HR: 0.67, 95%CI: 51 to 0.82 *vs* 0.94, 95%CI: 0.82 to 1.06; *P* = 0.01). Volume depletion was consistently increased in response to SGLT2i in all the subgroups.

CONCLUSION
Heart failure patients with lower LVEF and lower NYHA sub-classifications were found to be generally more likely to benefit from therapy with gliflozins. Further research are required to identify patient subgroups representing the highest benefits or adverse events in response to SGLT2i.

Key Words: Sodium glucose cotransporter 2 inhibitors; Cardiovascular; Renal outcome; efficacy; Heart failure with preserved ejection fraction; Heart failure with reduced ejection fraction

Core Tip: Compared to placebo, treatment with Sodium glucose cotransporter 2 inhibitors improve cardiorenal outcomes in a broad range of disorders with significant heterogeneity in the subgroup of patients who are likely to benefit most from the treatment across their heart failure subtypes, New York Heart Associations classifications and ejection fraction levels. There are also adverse events associated with these drugs that deserve further research.

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INTRODUCTION

Anti-hyperglycemic medications have been shown to improve cardiovascular outcomes and renal health in a range of disorders; yet in specific patient subpopulations there is a possibility that their side effects outweigh the protection they offer. For the same reason, large and expensive clinical trials have been conducted to investigate their impact on health entities, and protective roles have been reported for a number of these drugs that went beyond their antihyperglycemic effects[1,2].

Gliflozins or Sodium glucose cotransporter 2 inhibitors (SGLT2i) are relatively novel antidiabetic medications that lower blood levels of glucose through increasing its urinary excretion and therefore they also induce weight loss[1]. Recently a number of large clinical trials have shown significant cardiorenal protection by these drugs in a spectrum of diseases including patients with type 2 diabetes mellitus (T2DM), heart failure and chronic kidney diseases. However, the patient populations were inconsistent in these trials in several aspects, and there is a need for further research regarding the potential factors that might contribute in this effect. In fact, a number of systematic reviews have already been published covering a broad spectrum of cardiac, renal and metabolic factors, including meta-analyses showing significant improvements in the composite outcomes of cardiovascular death or hospitalizations in heart failure patients with either preserved (HFpEF) or reduced ejection fraction (HFrEF)[3-6]. The purpose of this systematic review and meta-analysis is to examine potential effects of SGLT2i therapy on the composite or specific cardiac or renal outcomes in heart failure patients across baseline left ventricular ejection fraction (LVEF) levels.

MATERIALS AND METHODS

Search strategy and selection criteria

Supplementary Figure 1 summarizes the search strategy of the current systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist was followed in this study (Supplementary Figure 2). A systematic search of the literature was performed using Cochrane Library, Reference Citation Analysis, nejm.org, and EuropePMC search engines to April 15, 2023. Pubmed/MEDLINE could not be reached due to internet filtering. Further search of the literature was performed using Google Scholar to find the *post hoc* analyses and substudies from the included large randomized controlled trials, regarding the subjects of interest for this systematic review (Figure 1).

In order to minimize potential publication biases, the inclusion criteria assigned eligibility only to the reports of double-blind and placebo-controlled trials if they were large (defined as at least 1000 subjects in the SLGT2i arm and at least half as many patients in the placebo arm) with long enough follow up time (at least 6 mo), assessing SGLT2i, and reported any of the efficacy or safety outcomes of interest in this review, as specified. Finally 27 studies (13 trials and 14

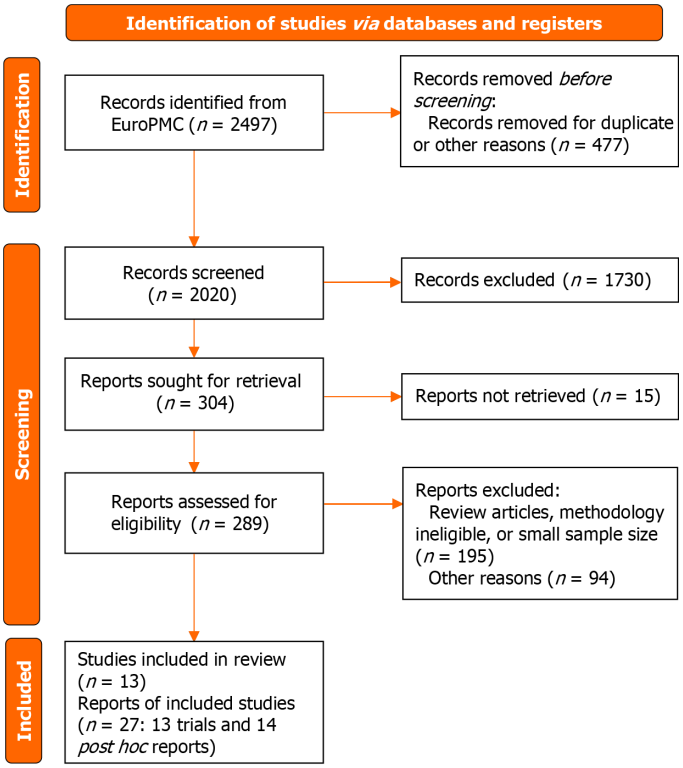

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Figure 1 PRISMA flow diagram.

post hoc analyses) were found and reviewed[7-33].

Outcomes of interest

The evaluated outcomes in this systematic review and meta-analysis included the primary composite outcome as defined by each study and irrespective of the disparities between them, cardiovascular death, the composite outcome of cardiovascular death or hospitalization (or an urgent visit) for heart failure, composite renal outcome (serious renal events defined by different studies and irrespective of potential differences between trials) and death from any cause.

Specific renal outcomes: As mentioned above, the composite renal outcomes were inconsistently defined by different studies and included a heterogeneous combinations of the following indicators: Doubling of serum creatinine measures, substantial decrease in estimated glomerular filtration rate (*i.e.* ≥ 40% decrease; falling below 60 to less than 15 mL/min/1.73 m^2 in different studies), end-stage kidney disease; renal replacement therapy initiation (*i.e.* dialysis or renal transplantation), and renal death. Wherever there were reports from more than one combination of renal outcomes, the one with the larger spectrum was used as the composite renal outcome for inclusion into the meta-analysis. Other renal outcomes that were evaluated in this study included renal disease progression/worsening renal function, acute kidney injury/acute renal failure, volume depletion, and diabetic ketoacidosis.

Stratifications across LVEF stratums

Heart failure subtypes: Data for primary outcomes of interests were extracted and meta-analysis were conducted across specific stratification strategies. The patients' heart failure status and the type of heart failure (*i.e.* HFpEF), HFrEF and mid-range/mildly-reduced ejection fraction (HFmrEF) were also extracted. The definition of HFpEF has varied across different trials, with HFpEF defined as EF > 40% in the EMPEROR-Preserved[16] and DELIVER[18], and as EF ≥ 50% in the SCORED[13], CANVAS[12], EMPA-REG OUTCOME[21], and SOLOIST-WHF[17] trials. Likewise, HFrEF was inconsistently defined as EF < 40% in the SCORED[13] and SOLOIST-WHF[17], as ≤ 40% in the EMPEROR-Reduced[15] and DAPA-HF[14], as EF < 45% in DECLARE-TIMI 58[33], as EF ≤ 45% in the VERTIS-CV[24], and as EF < 50% in the CANVAS[22] and EMPA-REG OUTCOME[21] trials. Heart failure with mildly reduced (mid-range) EF was consistently defined as EF between 40%-49%. Only in Supplementary Figure 3, LVEF rates between 35% and 55% were also considered HFmrEF. Finally, heart failure not-otherwise-specified (nos) as patients diagnosed with heart failure (presence of signs and symptoms of HF, elevated levels of natriuretic peptides in the plasma and evidence of structural heart disease - left ventricular hypertrophy or left atrial remodeling - or the presence of diastolic dysfunction) with no further stratifications. Patients who had baseline LVEF ranged within the definitions but without the documented diagnosis of heart failure were excluded from the respective subgroups.

LVEF stratums: Meta-analyses of the outcomes were repeated after stratification of the LVEF rates by LVEF stratums (*i.e.* documented heart failure patients with LVEF measures above or below the cutoff values of 30%, 40%, 45%, 50%, and

60%). However, since the outcome analyses across all the predefined LVEF cutoff points were not exactly performed by all the reviewed studies, an alternative approach was employed wherever there were reports that fell in ranges totally within the study subgroups defined across the cutoff points of this study; *e.g.* in meta-analysis of outcomes across LVEF of 40%, if a trial had only provided data of LVEF over 50% or below 30%, the data were included as LVEF over 40% or ≤ 40%, respectively (since LVEF values ≥ 50% falls totally within the range of > 40% and LVEF < 30% falls fully within the range of ≤ 40%). But data of patients with LVEF < 50% was not included into meta-analysis of patients with LVEF < 40%, since it doesn't totally fall within the specified range. Moreover, if data was available for two LVEF ranges for any particular study, both falling within the meta-analysis ranges, the one that was closest to the cutoff and therefore encompassed the largest possible patient population was chosen for inclusion (*e.g.* if LVEF > 45% and > 50% were available for a trial, in meta-analysis of outcomes across LVEF 40%, data of LVEF > 45% was included in the reports of LVEF > 40%).

Statistical analysis

Hazard ratio (HR) and 95% confidence interval (CI) were pooled using a random-effects DerSimonian and Laird model. Inverse of the variance was used to assign weights to each study. Heterogeneity among studies was assessed using the Higgins I^2 value. Meta-regression analysis was conducted using mixed-effects modelling to evaluate factors potentially explaining any observed heterogeneity for the study outcomes (*i.e.* composite study outcome, cardiovascular death and/or heart failure hospitalizations and composite or specific renal outcomes). Meta-regression models using demographic or disease-specific baseline data (*i.e.* age, gender, ethnicity, glycated hemoglobin, past medical history, *etc.*) inputs were not possible due the lack of the baseline data discriminately reported across the study groups (*i.e.* heart failure subtypes, LVEF cutoff levels and NYHA). The only factor that could be included into meta-regression without controversy was the type of gliflozins employed. Some other factors were also used for this purpose (including mean study follow-up time, T2DM and chronic kidney disease (CKD) as inclusion criterions to the study) which might sound controversial since the follow up times could be inconsistent in patient subgroups, as were T2DM and CKD status in studies not having them as inclusion criterions. Even though, no observed heterogeneity in any of the meta-analyses could be explained by the gliflozin type, with no significant effect returned by meta-regression analysis. The same observation was made for meta-regression analysis of the more controversial factors mentioned above.

No special dosage preferences were made for trials in which more than one SGLT2i dosage had been sought and the pooled effects were used for analyses wherever applicable and otherwise, data from the higher SGLT2i dosage was considered. Subgroup analysis was conducted to assess for variability of therapeutic effects across the LVEF stratums, heart failure subtypes and NYHA subclass populations. Study quality was assessed using version 2 of the Cochrane risk-of-bias tool. 2-tailed *P* values with statistical significance specified at 0.05 were used in all analyses. Stata version 17 (Stata Corp.) and Microsoft Excel 2013 (Microsoft Corp.) were used for analyses.

RESULTS

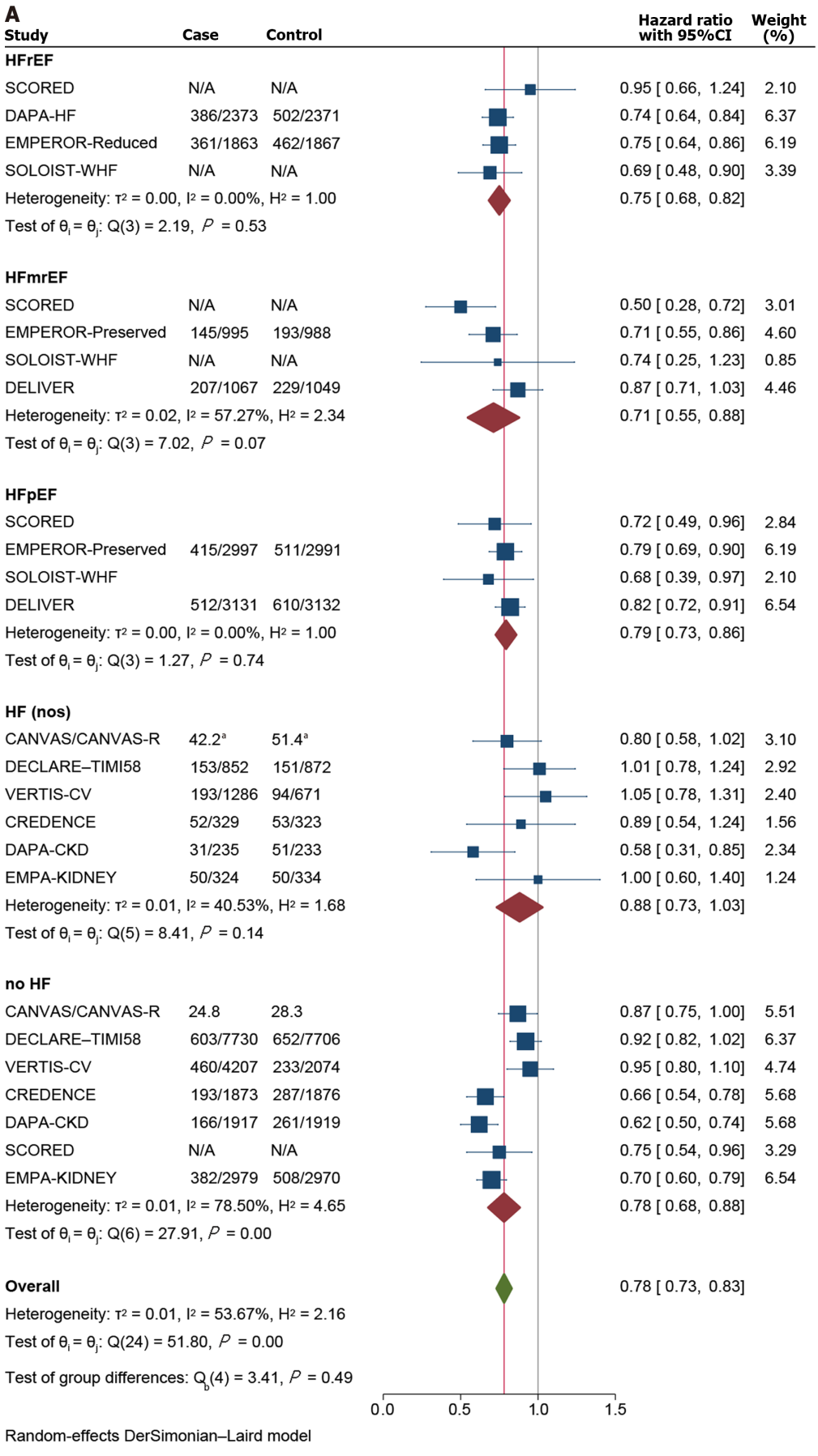
The literature search returned 13 large clinical trials evaluating impact of SGLT2i on the outcome of patients[7-19], and their characteristics are summarized in Table 1. Fourteen more studies reporting *post hoc* analysis of the reviewed trials were also found and reviewed[20-33]. Five trials were on heart failure patients, in seven trials only diabetic patients included and four trials were conducted specifically on patients with chronic kidney diseases. Patients' data and outcome reports were extracted regarding their heart failure status and included in the meta-analyses.

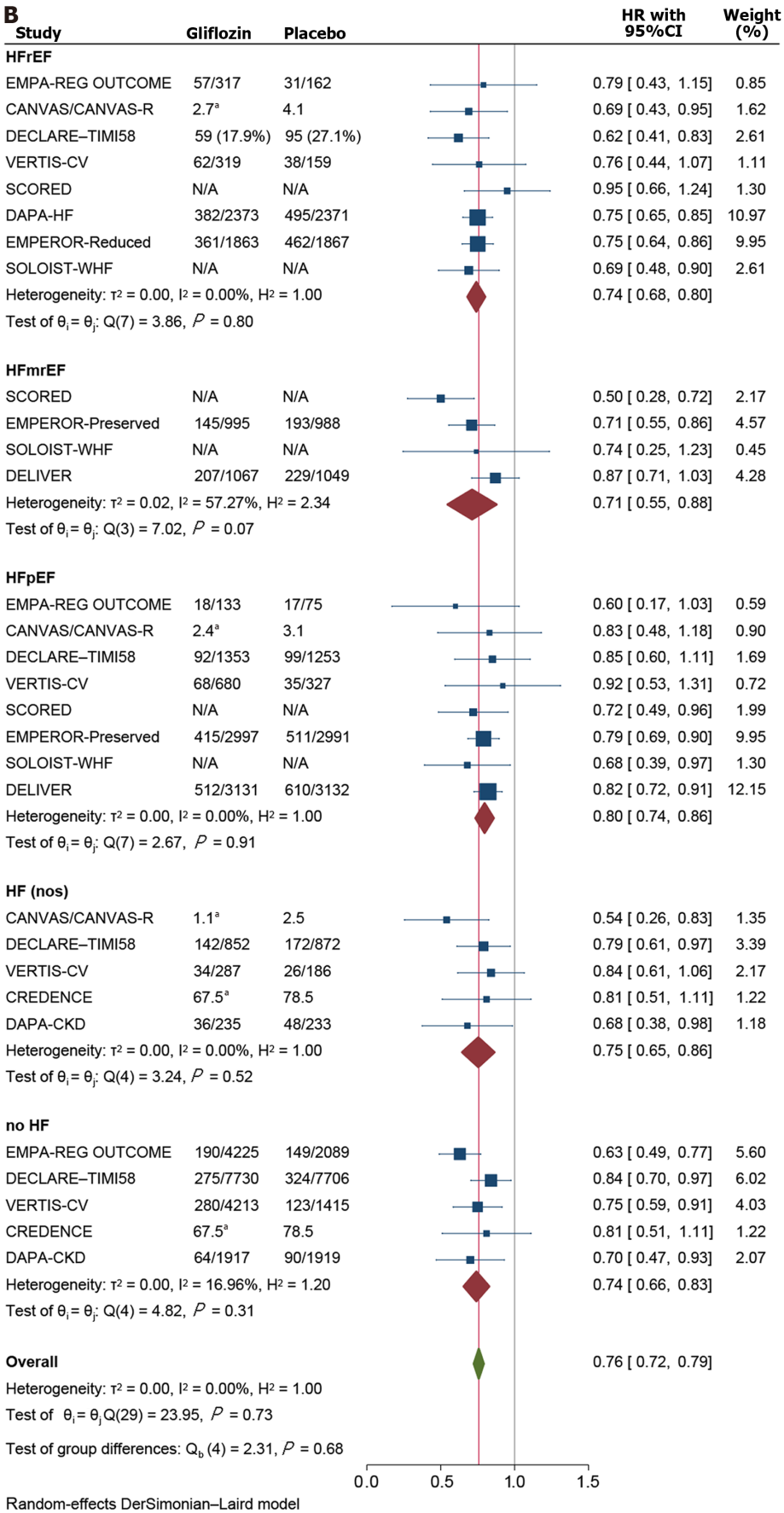
Meta-analyses across heart failure subtypes

Meta-analysis of the effects of gliflozins on the primary composite outcomes (cardiorenal events as defined by each study) showed that compared to placebo, SGLT2i significantly decreased the event rates (HR: 0.78, 95%CI: 0.73 to 0.83, I^2 = 53.7%), with no significant difference in efficacy across the heart failure status or subtypes (P = 0.49, Figure 2A). Likewise, when cardiovascular death and/or urgent visits/hospitalization for heart failure was used as the outcome, gliflozins were superior to placebo with no heterogeneity between the subgroups (HR: 0.76, 95%CI: 0.72 to 0.79, P = 0.68, I^2 = 0%, Figure 2B). Compared to placebo, SGLT2i therapy was again found to be significantly associated with lower cardiovascular death (HR: 0.84, 95%CI: 0.78 to 0.90, I^2 = 19.9%) and all-cause mortality (HR: 0.86, 95%CI: 0.81 to 0.91, I^2 = 32.1%), with no significant difference between the subgroups [P = 0.98 (Supplementary Figure 3) and P = 0.21 (Figure 3), respectively]. However, a trend toward higher effectiveness was observed for patients with HFrEF *vs* HFpEF; though it failed to reach the statistical significance just at the borderline level; P = 0.07 (Supplementary Figure 4).

Although no significant difference was detected in efficacy measures between the heart failure subtypes in any of the above-mentioned meta-analyses, interestingly SGLT2i seem to offer significant benefits in survival outcome (i.e. cardiovascular death or all-cause mortality) only to HFrEF or (to a lesser degree) HFmrEF patients, and the respective outcome effects did not reach significance level for HFpEF (HR: 0.89, 95%CI: 0.75 to 1.02; HR: 0.96, 95%CI: 0.88 to 1.05; respectively, Supplementary Figure 3 and Figure 3).

Meta-analyses of the primary composite outcomes across NYHA classes revealed significant improvement in the outcome rates [HR: 0.74(0.67-0.82)], although as is illustrated in Figure 4, this favorable effect was not consistent across all the NYHA subclasses and those at lower classes significantly better responded to SGLT2i (I^2 = 46%, P = 0.02; Figure 4).

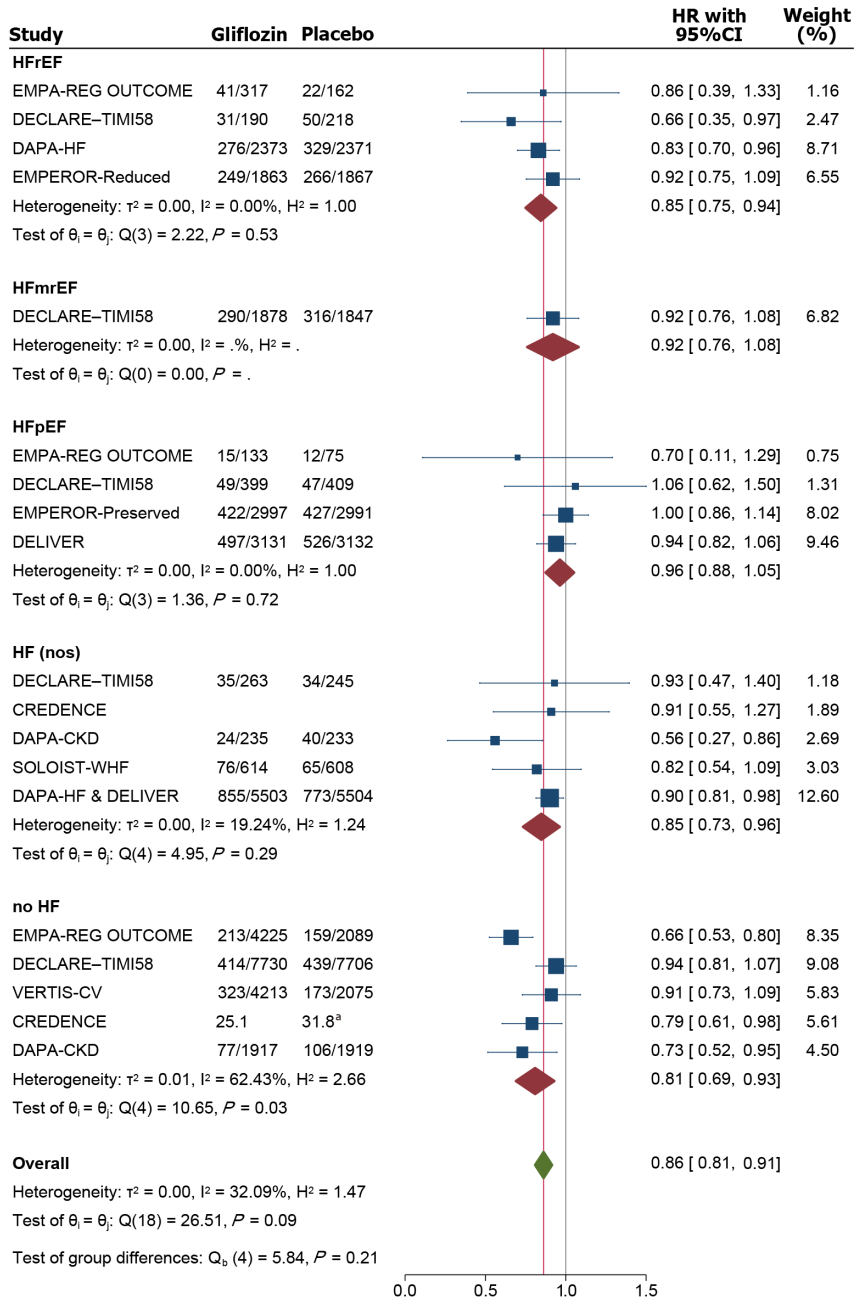

A
Study
Case
Control
Hazard ratio with 95%CI
Weight (%)
HFrEF
SCORED N/A N/A 0.95 [0.66, 1.24] 2.10
DAPA-HF 386/2373 502/2371 0.74 [0.64, 0.84] 6.37
EMPEROR-Reduced 361/1863 462/1867 0.75 [0.64, 0.86] 6.19
SOLOIST-WHF N/A N/A 0.69 [0.48, 0.90] 3.39
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.75 [0.68, 0.82]
Test of θi = θj: Q(3) = 2.19, P = 0.53
HFmrEF
SCORED N/A N/A 0.50 [0.28, 0.72] 3.01
EMPEROR-Preserved 145/995 193/988 0.71 [0.55, 0.86] 4.60
SOLOIST-WHF N/A N/A 0.74 [0.25, 1.23] 0.85
DELIVER 207/1067 229/1049 0.87 [0.71, 1.03] 4.46
Heterogeneity: τ² = 0.02, I² = 57.27%, H² = 2.34 0.71 [0.55, 0.88]
Test of θi = θj: Q(3) = 7.02, P = 0.07
HFpEF
SCORED 0.72 [0.49, 0.96] 2.84
EMPEROR-Preserved 415/2997 511/2991 0.79 [0.69, 0.90] 6.19
SOLOIST-WHF 0.68 [0.39, 0.97] 2.10
DELIVER 512/3131 610/3132 0.82 [0.72, 0.91] 6.54
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.79 [0.73, 0.86]
Test of θi = θj: Q(3) = 1.27, P = 0.74
HF (nos)
CANVAS/CANVAS-R 42.2[a] 51.4[a] 0.80 [0.58, 1.02] 3.10
DECLARE–TIMI58 153/852 151/872 1.01 [0.78, 1.24] 2.92
VERTIS-CV 193/1286 94/671 1.05 [0.78, 1.31] 2.40
CREDENCE 52/329 53/323 0.89 [0.54, 1.24] 1.56
DAPA-CKD 31/235 51/233 0.58 [0.31, 0.85] 2.34
EMPA-KIDNEY 50/324 50/334 1.00 [0.60, 1.40] 1.24
Heterogeneity: τ² = 0.01, I² = 40.53%, H² = 1.68 0.88 [0.73, 1.03]
Test of θi = θj: Q(5) = 8.41, P = 0.14
no HF
CANVAS/CANVAS-R 24.8 28.3 0.87 [0.75, 1.00] 5.51
DECLARE–TIMI58 603/7730 652/7706 0.92 [0.82, 1.02] 6.37
VERTIS-CV 460/4207 233/2074 0.95 [0.80, 1.10] 4.74
CREDENCE 193/1873 287/1876 0.66 [0.54, 0.78] 5.68
DAPA-CKD 166/1917 261/1919 0.62 [0.50, 0.74] 5.68
SCORED N/A N/A 0.75 [0.54, 0.96] 3.29
EMPA-KIDNEY 382/2979 508/2970 0.70 [0.60, 0.79] 6.54
Heterogeneity: τ² = 0.01, I² = 78.50%, H² = 4.65 0.78 [0.68, 0.88]
Test of θi = θj: Q(6) = 27.91, P = 0.00
Overall 0.78 [0.73, 0.83]
Heterogeneity: τ² = 0.01, I² = 53.67%, H² = 2.16
Test of θi = θj: Q(24) = 51.80, P = 0.00
Test of group differences: Qb(4) = 3.41, P = 0.49
0.0
0.5
1.0
1.5
Random-effects DerSimonian–Laird model



DOI: 10.5527/wjn.v12.i5.182

Figure 2 Meta-analysis of primary composite outcome. A: Gliflozins' effect on the primary composite outcome across heart failure subtypes; B: Gliflozins' effect on the composite outcome of 'cardiovascular deaths or hospitalizations due to heart failure or urgent visits' across heart failure subtypes. HF: Heart failure;

HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; nos: Not otherwise specified; N/A: Not available. [a]per 1000 person-years; [b]per 100 person-years.

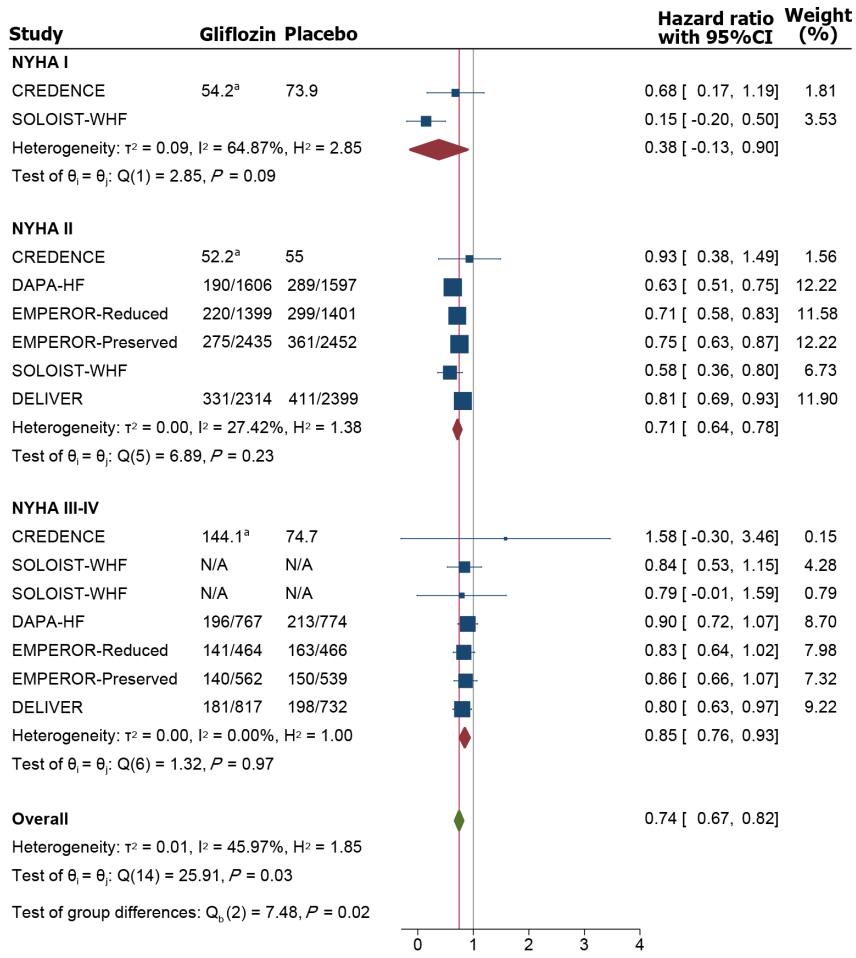


DOI: 10.5527/wjn.v12.i5.182

Figure 3 Meta-analysis of the effects of Sodium glucose cotransporter 2 inhibitors on the all-cause mortality across the heart failure subtypes. HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; nos: Not otherwise specified. [a]per 1000 person-years.

Meta-analysis across LVEF stratums

Meta-analyses were repeated across the LVEF stratums, irrespective of the authors' definitions of the heart failure subtypes. The primary composite outcomes across all the LVEF cutoff levels showed significant efficacy for gliflozins compared to placebo, with no significant difference between the subgroups. Notably, patients with a baseline LVEF of 30% or less represented enhanced improvement in the primary composite outcome compared to patients with LVEF over 30%, but at the borderline statistical significance (HR: 0.70, 95%CI: 0.60 to 0.79 *vs* 0.81, 95%CI: 0.75 to 0.87; respectively, $P = 0.06$; Supplementary Figure 4).



DOI: 10.5527/wjn.v12.i5.182

Figure 4 Meta-analysis of the effects of Sodium glucose cotransporter 2 inhibitors on the primary composite outcome of heart failure patients across different New York Heart Associations classifications. [a]per 1000 person-years.

Similar to the results of primary outcome analyses, meta-analysis of the composite outcome of 'cardiovascular death or hospitalizations (or urgent visits) due to heart failure' exhibited significant improvement in response to treatment with SGLT2i at all the LVEF levels though again, compared to patients with LVEF above 30%, the subgroup of patients with the baseline LVEF of 30% or less showed a stronger response to gliflozins at borderline significance (HR: 0.69, 95%CI: 0.61 to 0.76 *vs* 0.78, 95%CI: 0.71 to 0.85; $P = 0.07$). Further analyzes at higher cutoff values showed no significant difference for the respective outcome ($P > 0.4$ for all; Figure 5). All-cause mortality also showed significant benefit across LVEF stratums with the relatively best effect size in patients with LVEF ≤ 40% (versus LVEF > 40%) but no statistical significance was reached; Figure 6.

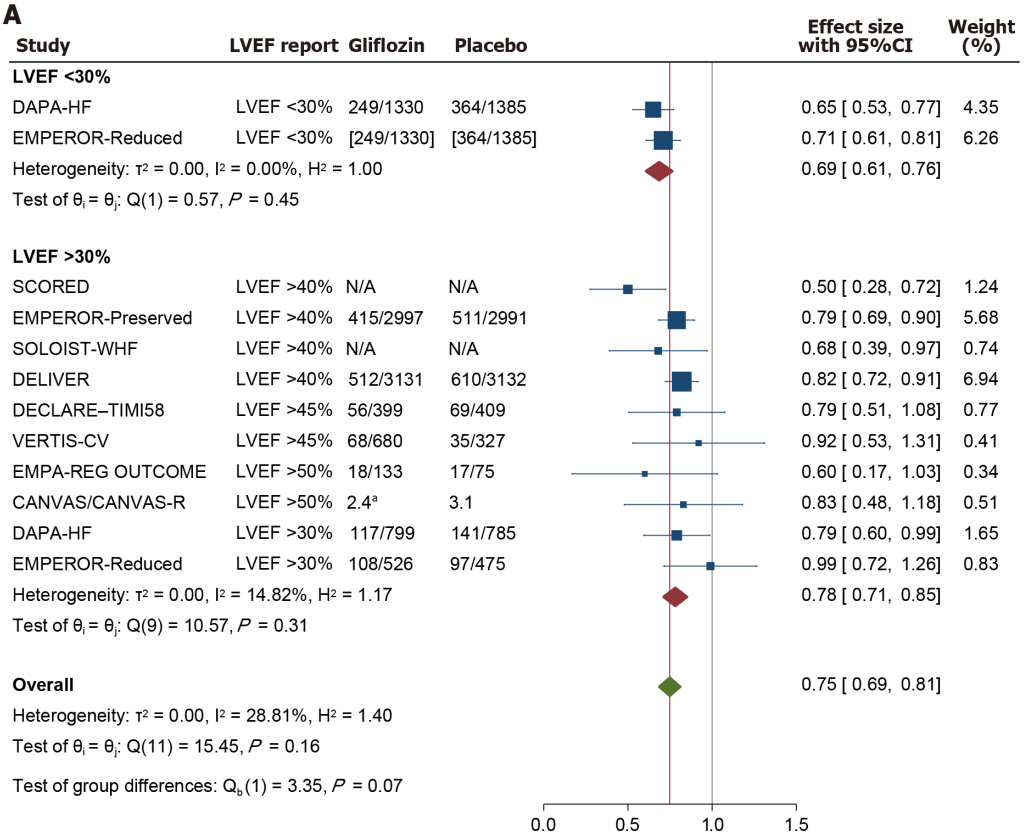
Renal outcome meta-analyses across heart failure subtypes

Composite renal events: Composite renal events was an unspecific terminology that comprised a diverse spectrum of unfavorable renal events (described in methods) As could be perceived from Figure 6A, SGLT2i significantly improved composite renal events as compared to the placebo-treated group (HR: 0.69, 95%CI: 0.59 to 0.79), but significant difference across the meta-analysis patient groups was observed with HFpEF and no-heart failure patients representing the lowest and the highest response rates, respectively (HR: 0.94, 95%CI: 0.74 to 1.13 and 0.60, 95%CI: 0.49 to 0.72, respectively); $P = 0.04$, Figure 7.

Acute kidney injury (or acute renal failure) was also shown to occure significantly less frequently in patients receiving SGLT2i compared to placebo (HR: 0.83, 95%CI: 0.75 to 0.92; Figure 7B); however this effect was not consistent across the heart failure groups and HFrEF and HFpEF patients respectively represented the highest and the lowest response rates with significant difference between, after excluding other subgroups from the meta-analysis (HR: 0.67, 95%CI: 51 to 0.82 *vs* 0.94, 95%CI: 0.82 to 1.06; $P = 0.01$, Supplementary Figure 5).

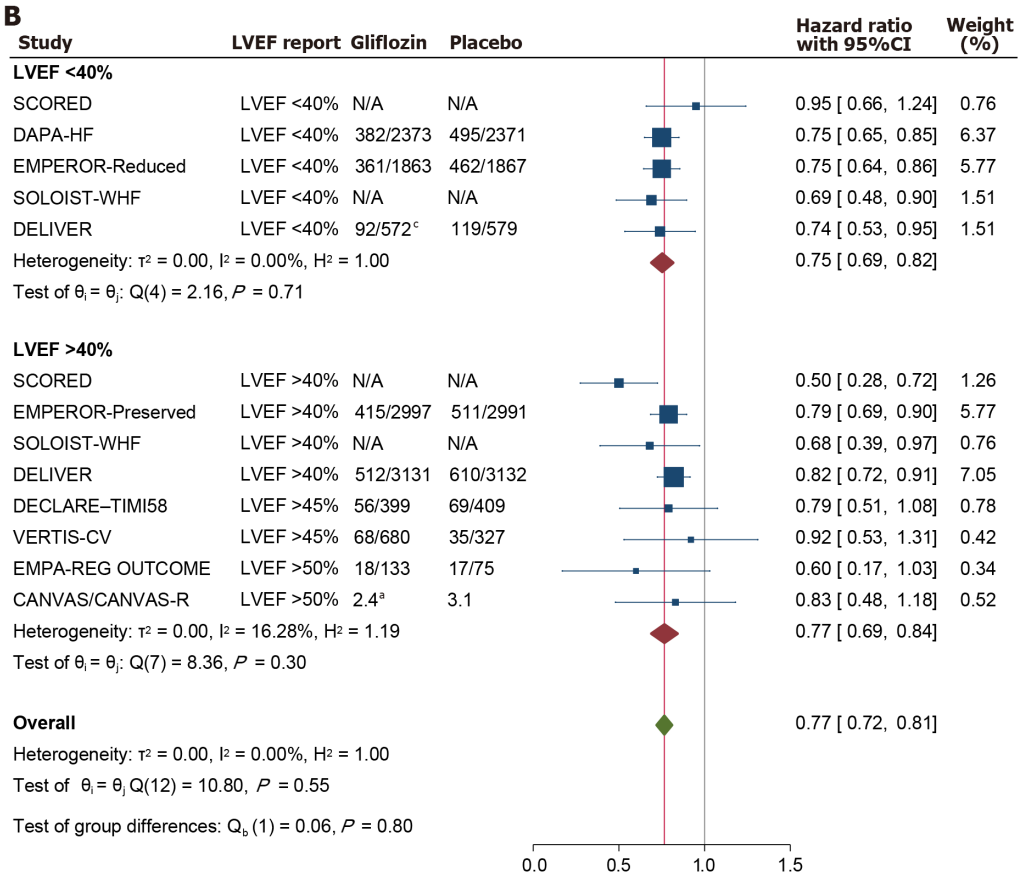
Renal disease progression or worsening renal function: Gliflozins significantly reduced renal disease progression in the meta-analysis (HR: 0.63, 95%CI: 0.55 to 0.71). But unlike the composite renal event, no significant difference was found regarding the heart failure status or across subtypes ($P = 0.52$; Supplementary Figure 6).

A



Random-effects DerSimonian–Laird model

B



Random-effects DerSimonian–Laird model

C

Study	LVEF report	Gliflozin	Placebo	Hazard ratio with 95%CI	Weight (%)
LVEF <45%					
SCORED	LVEF <40%	N/A	N/A	0.95 [0.66, 1.24]	0.76
DECLARE–TIMI58	LVEF <45%	59 (17.9%)	95 (27.1%)	0.62 [0.41, 0.83]	1.51
VERTIS-CV	LVEF <45%	62/319	38/159	0.76 [0.44, 1.07]	0.64
DAPA-HF plus DELIVER	LVEF <45%	473/2824	595/2784	0.81 [0.72, 0.90]	7.86
EMPEROR (both)	LVEF <45%	423/2253	537/2251	0.74 [0.63, 0.85]	5.77
Heterogeneity: τ^2 = 0.00, I^2 = 13.16%, H^2 = 1.15				0.77 [0.70, 0.84]	
Test of $\theta_i = \theta_j$: Q(4) = 4.61, P = 0.33					
LVEF >45%					
DECLARE–TIMI58	LVEF >45%	56/399	69/409	0.79 [0.51, 1.08]	0.78
VERTIS-CV	LVEF >45%	68/680	35/327	0.92 [0.53, 1.31]	0.42
EMPEROR-Preserved	LVEF >45%	353/2610	436/2607	0.78 [0.66, 0.90]	4.42
DELIVER	LVEF >45%	[440/2680]	[533/2687]	0.85 [0.75, 0.95]	6.37
EMPA-REG OUTCOME	LVEF >50%	18/133	17/75	0.60 [0.17, 1.03]	0.34
CANVAS/CANVAS-R	LVEF >50%	2.4[a]	3.1	0.83 [0.48, 1.18]	0.52
SCORED	LVEF >50%	.	.	0.72 [0.49, 0.96]	1.15
SOLOIST-WHF	LVEF >50%	30.6[b]	64	0.48 [0.18, 0.77]	0.73
DELIVER	LVEF >50%	305/2064	381/2083	0.81 [0.69, 0.93]	4.81
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00				0.80 [0.74, 0.85]	
Test of $\theta_i = \theta_j$: Q(8) = 7.28, P = 0.51					
Overall				0.79 [0.74, 0.83]	
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00					
Test of $\theta_i = \theta_j$: Q(13) = 12.20, P = 0.51					
Test of group differences: $Q_b(1)$ = 0.33, P = 0.57					

Random-effects DerSimonian–Laird model

D

Study	LVEF report	Gliflozin	Placebo	Hazard ratio with 95%CI	Weight (%)
LVEF <50%					
DAPA-HF	LVEF <40%	382/2373	495/2371	0.75 [0.65, 0.85]	6.37
EMPEROR-Reduced	LVEF <40%	361/1863	462/1867	0.75 [0.64, 0.86]	5.77
VERTIS-CV	LVEF <45%	62/319	38/159	0.76 [0.44, 1.07]	0.64
EMPA-REG OUTCOME	LVEF <50%	57/317	31/162	0.79 [0.43, 1.15]	0.49
CANVAS/CANVAS-R	LVEF <50%	2.7[a]	4.1	0.69 [0.43, 0.95]	0.94
SCORED	LVEF <50%	N/A	N/A	0.84 [0.61, 1.06]	1.26
EMPEROR-Preserved	LVEF <50%	145/995	193/988	0.71 [0.55, 0.86]	2.65
SOLOIST-WHF	LVEF <50%	56.9[b]	79.9	0.72 [0.53, 0.91]	1.76
DELIVER	LVEF <50%	207/1067	229/1049	0.87 [0.71, 1.03]	2.49
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00				0.76 [0.71, 0.81]	
Test of $\theta_i = \theta_j$: Q(8) = 3.25, P = 0.92					
LVEF >50%					
EMPA-REG OUTCOME	LVEF >50%	18/133	17/75	0.60 [0.17, 1.03]	0.34
CANVAS/CANVAS-R	LVEF >50%	2.4[a]	3.1	0.83 [0.48, 1.18]	0.52
SCORED	LVEF >50%	.	.	0.72 [0.49, 0.96]	1.15
EMPEROR-Preserved	LVEF >50%	270/2002	318/2003	0.83 [0.68, 0.97]	3.03
SOLOIST-WHF	LVEF >50%	30.6[b]	64	0.48 [0.18, 0.77]	0.73
DELIVER	LVEF >50%	305/2064	381/2083	0.81 [0.69, 0.93]	4.81
Heterogeneity: τ^2 = 0.00, I^2 = 12.10%, H^2 = 1.14				0.77 [0.68, 0.86]	
Test of $\theta_i = \theta_j$: Q(5) = 5.69, P = 0.34					
Overall				0.77 [0.72, 0.81]	
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00					
Test of $\theta_i = \theta_j$: Q(14) = 9.07, P = 0.83					
Test of group differences: Q_b (1) = 0.03, P = 0.85					

Random-effects DerSimonian–Laird model

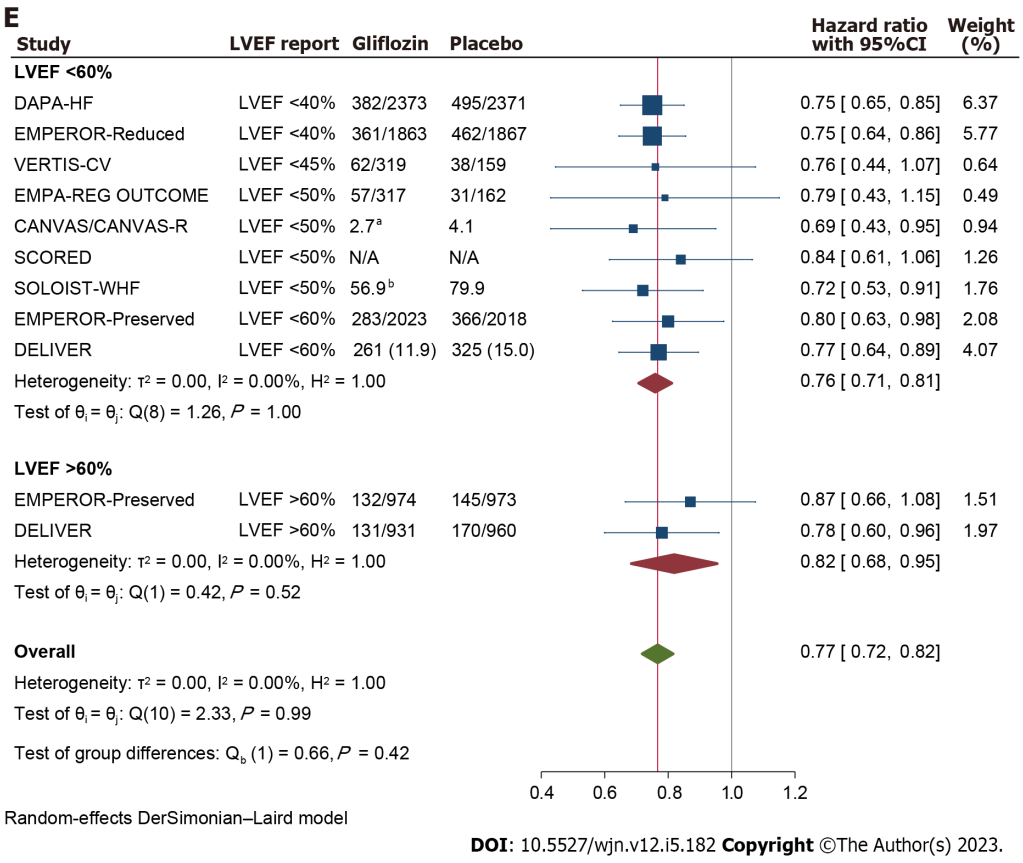


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Figure 5 Meta-analysis of Sodium glucose cotransporter 2 inhibitors' effect on 'cardiovascular death or heart failure hospitalizations or urgent visits' across the patients' baseline left ventricular ejection fraction strata. A: Left ventricular ejection fraction (LVEF) < 30% *vs* ≥ 30%; B: LVEF < 40% *vs* ≥ 40%; C: LVEF < 45% *vs* LVEF ≥ 45%; D: LVEF < 50% *vs* LVEF ≥ 50%; E: LVEF < 60% *vs* LVEF ≥ 60%. [a]per 1000 person-years; [b]per 100 person-years; [c]analysis based on the "history of previous LVEF < 40%" reported by DELIVER trial; LVEF: Left ventricular ejection fraction; N/A: Not available.

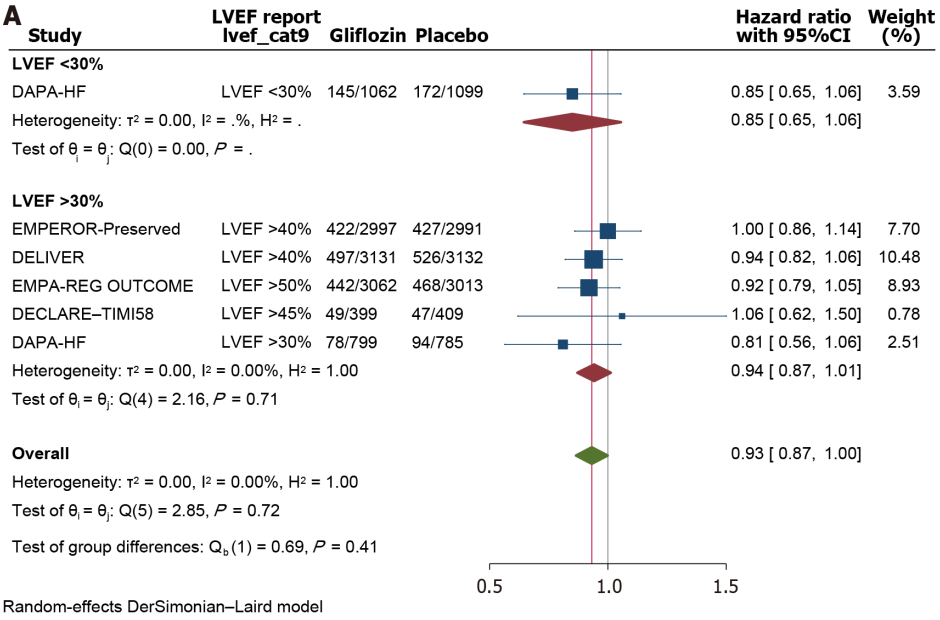
Volume depletion: As is evident from Supplementary Figure 7, SGLT2i therapy was associated with significantly higher rates of volume depletion in the pooled data meta-analysis with no significant difference across the study subgroups (HR: 1.14, 95%CI: 1.02 to 1.26; $P = 0.33$).

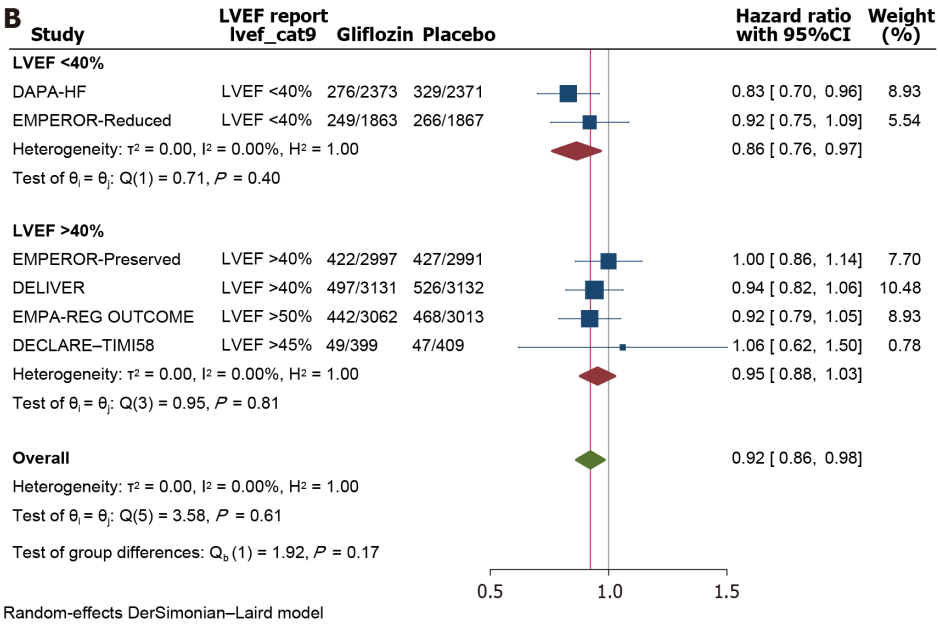
Diabetic ketoacidosis: As is summarized in Supplementary Table 1, diabetic ketoacidosis was a rare observation in both the SGLT2i and placebo groups, and therefore meta-analyses were not possible. The distribution of the outcomes between the two groups reveals no heterogeneity.

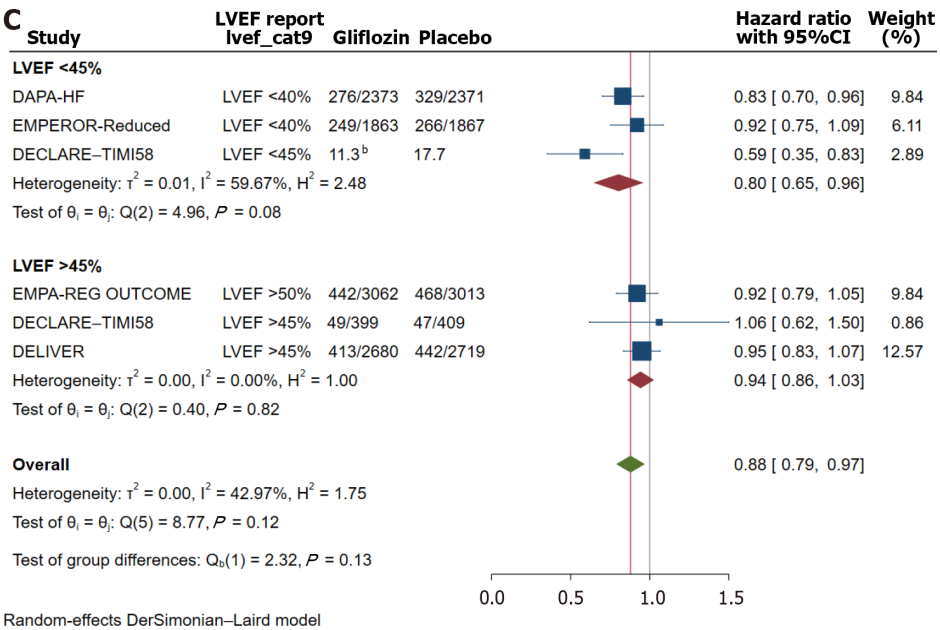
DISCUSSION

In this meta-analysis of 13 large clinical trials, data of 45918 patients were screened and significant but inequivalent protective effects for SGLT2i were found across the patients' LVEF strata, regarding a spectrum of cardiovascular and renal outcomes. Compared to HFpEF patients, HFrEF exhibited more dramatic response to gliflozins in a good number of the predefined outcomes. This finding is in contrast to a previous study in which authors found equivalent efficacy in heart failure patients across a full spectrum of LVEF[30]. One reason for this disparity could be related to the number of studies and patients entered into the analysis, with the current study encompassing substantially larger population (including data from the mentioned study). As well, in the current study the analyses were performed across different cutoff points compared to the analyses across the spectrum of LVEF, which leaves only a limited number of subjects for each subgroup. Moreover the spectrum of specific outcomes investigated in the current study was relatively broader.

Previous review articles have explored several predicting factors on response to SGLT2i. In a comprehensive review, Baigent *et al*[20] analyzed the impact of diabetes mellitus on the cardiorenal protective effects of SGLT2i treatment and found no disparity regarding diabetes status. In another review study, Zelniker *et al*[2] reported that the cardiovascular benefits of gliflozins in diabetic population seem to be largely confined to patients with established atherosclerotic cardiovascular disease. Bhatia *et al*[34] provided evidence for SGLT2i protective effects in a broader range of cardiac, renal and metabolic derangements, and in another very recent *post hoc* analysis from DELIVER trial, Peikert *et al*[35] reported substantial improvements in a large range of symptoms, functionality indices, and quality of life in HFmrEF/HFpEF patients in response to SGLT2i. The current systematic review provides further data on the variability of response


A
Study
LVEF report lvef_cat9
Gliflozin
Placebo
Hazard ratio with 95%CI
Weight (%)
LVEF <30%
DAPA-HF LVEF <30% 145/1062 172/1099 0.85 [0.65, 1.06] 3.59
Heterogeneity: τ² = 0.00, I² = .%, H² = . 0.85 [0.65, 1.06]
Test of θi = θj: Q(0) = 0.00, P = .
LVEF >30%
EMPEROR-Preserved LVEF >40% 422/2997 427/2991 1.00 [0.86, 1.14] 7.70
DELIVER LVEF >40% 497/3131 526/3132 0.94 [0.82, 1.06] 10.48
EMPA-REG OUTCOME LVEF >50% 442/3062 468/3013 0.92 [0.79, 1.05] 8.93
DECLARE–TIMI58 LVEF >45% 49/399 47/409 1.06 [0.62, 1.50] 0.78
DAPA-HF LVEF >30% 78/799 94/785 0.81 [0.56, 1.06] 2.51
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.94 [0.87, 1.01]
Test of θi = θj: Q(4) = 2.16, P = 0.71
Overall 0.93 [0.87, 1.00]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(5) = 2.85, P = 0.72
Test of group differences: Qb(1) = 0.69, P = 0.41
0.5
1.0
1.5
Random-effects DerSimonian–Laird model


B
Study
LVEF report lvef_cat9
Gliflozin
Placebo
Hazard ratio with 95%CI
Weight (%)
LVEF <40%
DAPA-HF LVEF <40% 276/2373 329/2371 0.83 [0.70, 0.96] 8.93
EMPEROR-Reduced LVEF <40% 249/1863 266/1867 0.92 [0.75, 1.09] 5.54
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.86 [0.76, 0.97]
Test of θi = θj: Q(1) = 0.71, P = 0.40
LVEF >40%
EMPEROR-Preserved LVEF >40% 422/2997 427/2991 1.00 [0.86, 1.14] 7.70
DELIVER LVEF >40% 497/3131 526/3132 0.94 [0.82, 1.06] 10.48
EMPA-REG OUTCOME LVEF >50% 442/3062 468/3013 0.92 [0.79, 1.05] 8.93
DECLARE–TIMI58 LVEF >45% 49/399 47/409 1.06 [0.62, 1.50] 0.78
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.95 [0.88, 1.03]
Test of θi = θj: Q(3) = 0.95, P = 0.81
Overall 0.92 [0.86, 0.98]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(5) = 3.58, P = 0.61
Test of group differences: Qb(1) = 1.92, P = 0.17
0.5
1.0
1.5
Random-effects DerSimonian–Laird model


C
Study
LVEF report lvef_cat9
Gliflozin
Placebo
Hazard ratio with 95%CI
Weight (%)
LVEF <45%
DAPA-HF LVEF <40% 276/2373 329/2371 0.83 [0.70, 0.96] 9.84
EMPEROR-Reduced LVEF <40% 249/1863 266/1867 0.92 [0.75, 1.09] 6.11
DECLARE–TIMI58 LVEF <45% 11.3[b] 17.7 0.59 [0.35, 0.83] 2.89
Heterogeneity: τ² = 0.01, I² = 59.67%, H² = 2.48 0.80 [0.65, 0.96]
Test of θi = θj: Q(2) = 4.96, P = 0.08
LVEF >45%
EMPA-REG OUTCOME LVEF >50% 442/3062 468/3013 0.92 [0.79, 1.05] 9.84
DECLARE–TIMI58 LVEF >45% 49/399 47/409 1.06 [0.62, 1.50] 0.86
DELIVER LVEF >45% 413/2680 442/2719 0.95 [0.83, 1.07] 12.57
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.94 [0.86, 1.03]
Test of θi = θj: Q(2) = 0.40, P = 0.82
Overall 0.88 [0.79, 0.97]
Heterogeneity: τ² = 0.00, I² = 42.97%, H² = 1.75
Test of θi = θj: Q(5) = 8.77, P = 0.12
Test of group differences: Qb(1) = 2.32, P = 0.13
0.0
0.5
1.0
1.5
Random-effects DerSimonian–Laird model

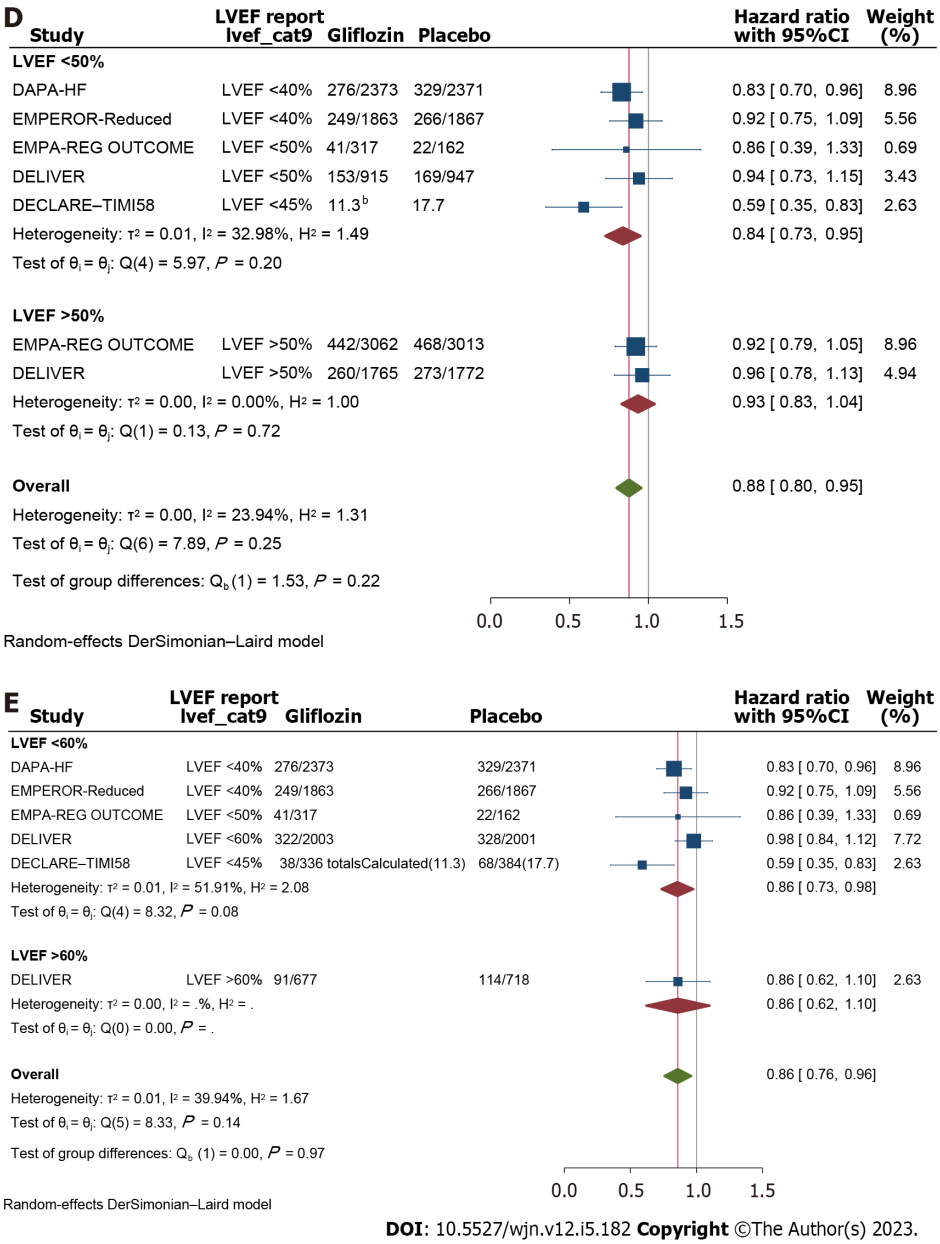


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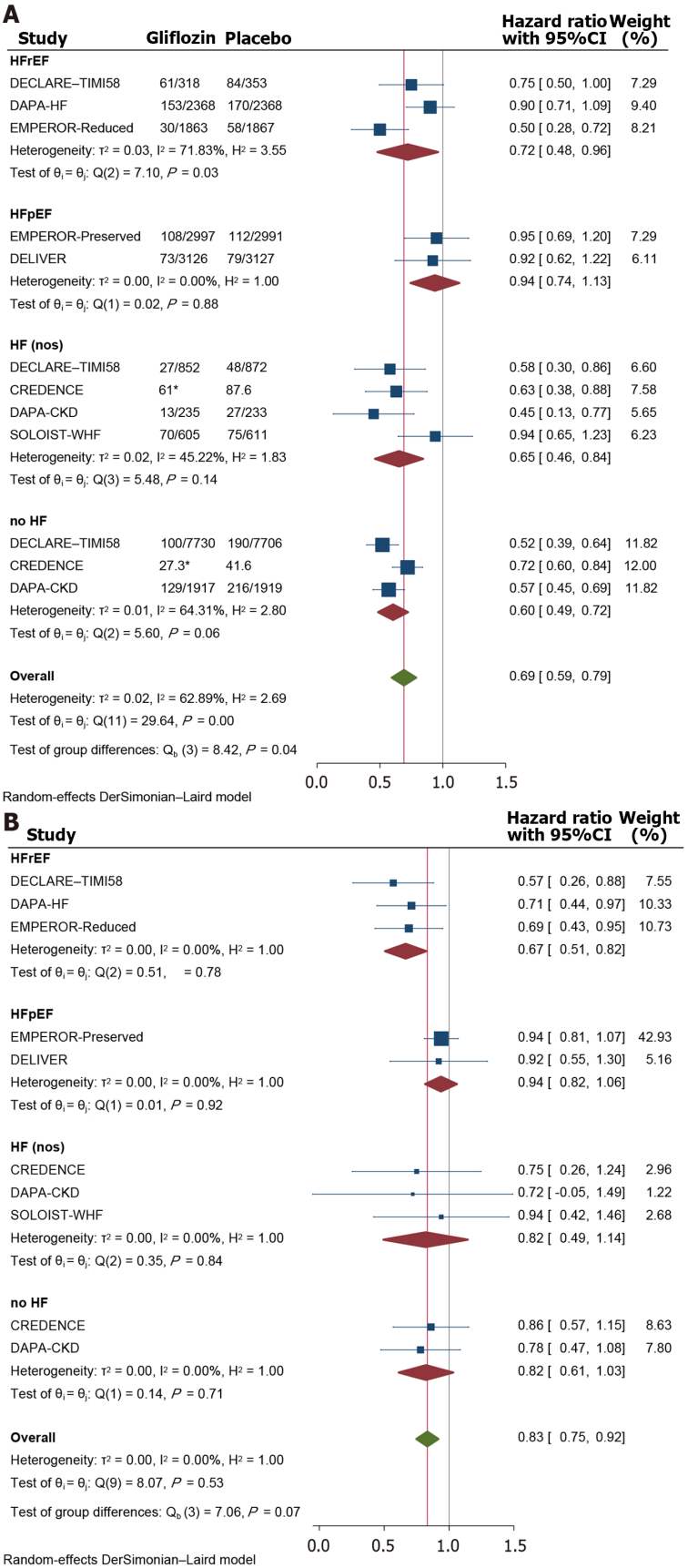
Figure 6 Meta-analysis of gliflozins' effect on the all-cause mortality across left ventricular ejection fraction strata (versus placebo). A: Left ventricular ejection fraction (LVEF) ≤ 30% *vs* > 30%; B: LVEF ≤ 40% *vs* > 40%; C: LVEF ≤ 45% *vs* LVEF > 45%; D: LVEF ≤ 50% *vs* LVEF > 50%; E: LVEF ≤ 60% *vs* LVEF > 60%. [b]per 100 person-years. LVEF: Left ventricular ejection fraction; N/A: Not available.

to gliflozins in heart failure patients regarding their LVEF levels and NYHA classifications, which could have significant clinical implications for the practitioners.

It is noteworthy that all the clinical trials reviewed in this study have compared the outcome of patients receiving gliflozins *vs* placebo. Although this verifies favorable effects for the drug, it doesn't provide robust evidence that this protective effect outweighs the advantages that are expectable from conventional medications prescribed in this patients; therefore it is still an open question as to whether or not gliflozins' protection outweighs the conventional medications or is there some sort of synergistic relationship between them. But this was out of the scope of the current systematic review, and future studies are required to issue this questions.

Cardiac outcomes: Gliflozins significantly improved the primary composite outcome of cardiovascular death and hospitalizations in patients with or without heart failure and across all the subgroups. However this effect seemed to be skewed in favor of HFrEF compared to HFpEF (the number of patients needed to be treated to save one additional patient from the primary composite outcome in the HFpEF was twice as large as the HFrEF in CANVAS/CANVAS-R trial[22] and 2.9 times for EMPEROR-Reduced *vs* either EMPEROR-Preserved or DELIVER[16,18]; this result was not reproduced in EMPA-REG OUTCOME trial[21]). Reanalyses of the patients' composite outcomes as described above (*i.e.* cardiovascular death or associated hospitalizations) were based on arbitrary definitions of heart failure subgroups by LVEF levels, inconsistently made by the authors in the different trials; therefore in order to have more precise conclusions, definitive cutoff points across LVEF were set and sought for the evaluation of the outcome, and it has been revealed that for a



DOI: 10.5527/wjn.v12.i5.182

Figure 7 Meta-analysis of the Sodium glucose cotransporter 2 inhibitors' effect on different renal outcome indices across heart failure subtypes. A: Composite renaloutcome; B: Acute kidney injury. HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; nos: Not otherwise specified.

Table 1 Summary of the reviewed trials

Ref.	Ref-post-hoc	Trial	Year	Follow (yr)	N	Participants	Diabetes proportion %	Heart failure proportion (%)	SGLT2i	Primary outcome
[7]	21	EMPA-REG OUTCOME	2015	3.1	7020	T2DM with established CVD; eGFR ≥ 30 mL/min/1.73 m^2	7020 (100)	706 (10)	Empagliflozin	CV death+non-fatal MI+non-fatal stroke
[8]	22	CANVAS/CANVAS-R	2017	2.4	10142	T2DM with CVD or multiple RFs for CVD; eGFR ≥ 30 mL/min/1.73 m^2	10142 (100)	1461 (14)	Canagliflozin	CV death+non-fatal MI+non-fatal stroke
[9]	23	DECLARE–TIMI58	2019	4.2	17160	T2DM with CVD or multiple RFs for CVD	17160 (100)	1724 (10)	Dapagliflozin	CV death+MI+ischemic stroke
[10]	24	VERTIS-CV	2020	3.5	8246	T2DM with established CVD; eGFR ≥ 30 mL/min/1.73 m^2	8246 (100)	1958 (24)	Ertugliflozin	CV death+non-fatal MI+non-fatal stroke
[11]	25	CREDENCE	2019	2.6	4401	T2DM with CVD+albuminuria (uACR 300–5000); eGFR 30–90 mL/min/1.73 m^2	4401 (100)	652 (15)	Canagliflozin	ESKD, doubling of serum creatinine/death from renal/CV cause
[12]	26, 27	DAPA-CKD	2020	2.4	4304	CVD + albuminuria +/- T2DM (eGFR 25-75 mL/min/1.73 m^2)	2906 (68)	468 (11)	Dapagliflozin	ESKD, sustained ≥ 50% eGFR decline, death from renal or CV cause
[13]	-	SCORED	2020	1.3	10584	T2DM with CVD & RFs for CVD; (GFR) of 30 to 60 mL/min/1.73 m^2	10 584 (100)	3283 (31)	Sotagliflozin	CV death and hospitalizations and urgent visits for HF
[14]	28, 29	DAPA-HF	2019	1.5	4744	HF (EF ≤ 40% & NYHA class II–IV) +/- T2DM; eGFR ≥ 30 mL/min/1.73 m^2	2139 (45)	4744 (100)	Dapagliflozin	Worsening HF and CV death
[15]	31	EMPEROR-Reduced	2020	1.3	3730	HF (EF ≤ 40% & NYHA class II–IV) +/- T2DM	1856 (50)	3730 (100)	Empagliflozin	Composite of HF hospitalization and CV death
[16]		EMPEROR-Preserved	2021	26.2 months	5988	HF (EF > 40% & NYHA class II–IV) +/- T2DM; eGFR ≥ 20 mL/min/1.73 m^2	2938 (49)	5988 (100)	Empagliflozin	Composite of cardiovascular death or hospitalization for HF
[17]	32	SOLOIST-WHF	2020	0.75	1222	T2DM & recent hospitalization for HF; eGFR ≥ 30 mL/min/1.73 m^2	1222 (100)	1222 (100)	Sotagliflozin	CV death and hospitalizations and urgent visits for HF
[18]	30	DELIVER	2022	2.3	6263	HF (EF > 40% & NYHA class II–IV) +/- T2DM	3150 (50)	6263 (100)	Dapagliflozin	Hospitalization for HF or an urgent visit for HF or CV death
[19]		EMPA-KIDNEY	2023	2.0	6609	CKD [eGFR > 20 & < 45 OR 45 < eGFR < 90 mL/min/1.73 m^2 & (proteinuria)]	3040 (46)	658 (10)	Empagliflozin	eGFR to < 10 OR decrease in eGFR of ≥ 40% OR renal death

CKD: Chronic kidney disease; CV: Cardiovascular; CVD: Cardiovascular disease; EF: Ejection fraction; eGFR: Esetimated glomerular filtration rate; HF: Heart failure; MI: myocardial infarction; NYHA: New York Hear Associations classification of heart failure; RF: Risk factor; T2DM: Type 2 diabetes mellitus; SGLT2i: Sodium glucose cotransporter 2 inhibitors; NYHA: New York Heart Associations.

number of major outcomes, the benefit from SGLT2i therapy reaches significant difference in favor of the patients with lower LVEF, at the cutoff point of 30% (Supplementary Figure 4 and Figure 5). Interestingly, repeating the meta-analysis across NYHA classifications showed significantly enhanced therapeutic effects for patients at lower *vs* higher NYHA subclasses. These findings broaden our understanding on the subgroups of the heart failure patients who are likely to benefit most from the SGLT2i.

Death outcomes: Meta-analysis of the impact of SGLT2i on cardiovascular death and all-cause mortality also exhibited benefit with relative but none-significant difference between the subgroups (Figures 3 and 6 and Supplementary Figure 3). No significant survival benefit was detected for patients with HFpEF or in meta-analysis of data from patients with LVEF over 40%. For patients with HFmrEF, gliflozins failed to improve all-cause mortality but improved cardiovascular death just at the borderline significance (Figure 3 and Supplementary Figure 3). This findings rule out SGLT2i as a life-saving medication for HFpEF, and adds it to the list of drugs that have failed to extend life in these tough-to-treat patient population.

Renal specific outcom: Renal outcomes are of special interest in patients with either heart failure or diabetes mellitus and a main focus of attention in most of the reviewed trials. Although previous systematic reviews have shown the benefits of SGLT2i on renal events[20], potential variability in the magnitude of this protection across LVEF rates could have clinical implcations. Interestingly, results of the meta-analysis of composite renal outcomes were consistent with the respective analyses on the cardiovascular outcomes, with the HFrEF patients responding relatively but not significantly better to the treatment than HFpEF, though with an unexpected finding of detecting the most pronounced renal protective effects in patients without heart failure (Figure 7A). This offers that gliflozins' renoprotective effects are unlikely to be associated with their heart failure modifying effects and deserves further investigations.

In the meta-analyses of more specific renal outcomes, acute kidney injury was reduced by 32% in patients with HFrEF compared to only 6% in HFpEF, a difference that was statistically significant (Figure 7B). On the other hand, not every specific renal outcome benefited by SGLT2i, and volume depletion had been shown to be significantly exacerbated by 14% compared to patients receiving placebo. This finding warns of the possible risks to patients receiving gliflozins and emphasisthe need for close monitoring of patients for signs of volume depletion.

Limitations and strengths: There are strengths and limitations associated with this study that warrants further discussion. Different patient populations (exclusive inclusion of patients with diabetes mellitus, chronic kidney disease or heart failure, or variations in the proportions of these patients in different studies), large variations in the follow up times, and inconsistencies in the outcome definitions and reports between the reviewed trials are a number of limitations that could undermine the findings of this study. The principle strength of the current systematic review is providing a stratified outcome analysis across the LVEF stratums of patients with heart failure, and introducing the patient subgroups that are most or least likely to benefit from treatment with gliflozins. Identifying the patient populations that don't benefit the treatment gives a message to the scientific community that further research and developments are needed.

CONCLUSION

In conclusion, compared to placebo, SGLT2i have shown significant therapeutic effects in patients with or without heart failure regarding cardiovascular and renal outcomes. These effects are generally more pronounced in HFrEF patients at the lowest LVEF levels compared to HFpEF, with no survival advantage for the latter group. Patients with lower NYHA classifications were also found to respond more vigorously to the study drugs. Further well-designed studies are needed to determine other potential factors with significant roles in response to gliflozins.

ARTICLE HIGHLIGHTS

Research background

Gliflozins have been shown effective to improve outcomes in patients with heart failure.

Research motivation

Finding the indications for the prescription of gliflozins would help to concentrate research on subgroups that need further research and novel therapeutic approach.

Research objectives

To find the subpopulations of heart failure patients that benefit most from Sodium glucose cotransporter 2 (SGLT2) inhibitors based on their left ventricular ejection fraction levels.

Research methods

A systematic review and meta-analysis of data of patients receiving gliflozin thepay in large and robust randomized double-blind placebo trials was conducted. Meta-analyses were conducted after stratification of the patients based on their left ventricular ejection fraction (LVEF) levels.

Research results
Gliflozins were generally superior to placebo in improving composite outcome of patients with heart failure across LVEF levels. This therapeutic effects were more pronounced in patients with reduced LVEF and low New York Heart Associations classes. No survival benefit was detected for patients with preserved ejection fraction disease.

Research conclusions
Gliflozins are effective in improving the outcome in patients with heart failure.

Research perspectives
Further research would be needed to examine the magnitude of gliflozins' efficacy as well as its cost-effectiveness compared to the other therapeutic options in this patient population.

FOOTNOTES

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REFERENCES

1 **Braunwald E**. Gliflozins in the Management of Cardiovascular Disease. *N Engl J Med* 2022; **386**: 2024-2034 [PMID: 35613023 DOI: 10.1056/NEJMra2115011]
2 **Zelniker TA**, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019; **393**: 31-39 [PMID: 30424892 DOI: 10.1016/S0140-6736(18)32590-X]
3 **Gager GM**, Gelbenegger G, Jilma B, von Lewinski D, Sourij H, Eyileten C, Filipiak K, Postula M, Siller-Matula JM. Cardiovascular Outcome in Patients Treated With SGLT2 Inhibitors for Heart Failure: A Meta-Analysis. *Front Cardiovasc Med* 2021; **8**: 691907 [PMID: 34336954 DOI: 10.3389/fcvm.2021.691907]
4 **Herrington WG**, Savarese G, Haynes R, Marx N, Mellbin L, Lund LH, Dendale P, Seferovic P, Rosano G, Staplin N, Baigent C, Cosentino F. Cardiac, renal, and metabolic effects of sodium-glucose co-transporter 2 inhibitors: a position paper from the European Society of Cardiology ad-hoc task force on sodium-glucose co-transporter 2 inhibitors. *Eur J Heart Fail* 2021; **23**: 1260-1275 [PMID: 34184823 DOI: 10.1002/ejhf.2286]
5 **Tsampasian V**, Elghazaly H, Chattopadhyay R, Ali O, Corballis N, Chousou PA, Clark A, Garg P, Vassiliou VS. Sodium glucose co-transporter 2 inhibitors in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2022; **29**: e227-e229 [PMID: 34850881 DOI: 10.1093/eurjpc/zwab189]
6 **Banerjee M**, Pal R, Nair K, Mukhopadhyay S. SGLT2 inhibitors and cardiovascular outcomes in heart failure with mildly reduced and preserved ejection fraction: A systematic review and meta-analysis. *Indian Heart J* 2023; **75**: 122-127 [PMID: 36914068 DOI: 10.1016/j.ihj.2023.03.003]
7 **Wanner C**, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B; EMPA-REG OUTCOME Investigators. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med* 2016; **375**: 323-334 [PMID: 27299675 DOI: 10.1056/NEJMoa1515920]
8 **Neal B**, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017; **377**: 644-657 [PMID: 28605608 DOI: 10.1056/NEJMoa1611925]
9 **Wiviott SD**, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE–TIMI 58

Investigators. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2019; **380**: 347-357 [PMID: 30415602 DOI: 10.1056/NEJMoa1812389]

10 **Cannon CP**, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, Charbonnel B, Frederich R, Gallo S, Cosentino F, Shih WJ, Gantz I, Terra SG, Cherney DZI, McGuire DK; VERTIS CV Investigators. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. *N Engl J Med* 2020; **383**: 1425-1435 [PMID: 32966714 DOI: 10.1056/NEJMoa2004967]

11 **Perkovic V**, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 2019; **380**: 2295-2306 [PMID: 30990260 DOI: 10.1056/NEJMoa1811744]

12 **Heerspink HJL**, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Wheeler DC; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 2020; **383**: 1436-1446 [PMID: 32970396 DOI: 10.1056/NEJMoa2024816]

13 **Bhatt DL**, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Inzucchi SE, Kosiborod MN, Cherney DZI, Dwyer JP, Scirica BM, Bailey CJ, Díaz R, Ray KK, Udell JA, Lopes RD, Lapuerta P, Steg PG; SCORED Investigators. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. *N Engl J Med* 2021; **384**: 129-139 [PMID: 33200891 DOI: 10.1056/NEJMoa2030186]

14 **McMurray JJV**, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM; DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019; **381**: 1995-2008 [PMID: 31535829 DOI: 10.1056/NEJMoa1911303]

15 **Packer M**, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F; EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020; **383**: 1413-1424 [PMID: 32865377 DOI: 10.1056/NEJMoa2022190]

16 **Anker SD**, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M; EMPEROR-Preserved Trial Investigators. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med* 2021; **385**: 1451-1461 [PMID: 34449189 DOI: 10.1056/NEJMoa2107038]

17 **Bhatt DL**, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Voors AA, Metra M, Lund LH, Komajda M, Testani JM, Wilcox CS, Ponikowski P, Lopes RD, Verma S, Lapuerta P, Pitt B; SOLOIST-WHF Trial Investigators. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med* 2021; **384**: 117-128 [PMID: 33200892 DOI: 10.1056/NEJMoa2030183]

18 **Solomon SD**, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, Jhund PS, Belohlavek J, Chiang CE, Borleffs CJW, Comin-Colet J, Dobreanu D, Drozdz J, Fang JC, Alcocer-Gamba MA, Al Habeeb W, Han Y, Cabrera Honorio JW, Janssens SP, Katova T, Kitakaze M, Merkely B, O'Meara E, Saraiva JFK, Tereshchenko SN, Thierer J, Vaduganathan M, Vardeny O, Verma S, Pham VN, Wilderäng U, Zaozerska N, Bachus E, Lindholm D, Petersson M, Langkilde AM; DELIVER Trial Committees and Investigators. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med* 2022; **387**: 1089-1098 [PMID: 36027570 DOI: 10.1056/NEJMoa2206286]

19 **The EMPA-KIDNEY Collaborative Group**, Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, Preiss D, Judge P, Mayne KJ, Ng SYA, Sammons E, Zhu D, Hill M, Stevens W, Wallendszus K, Brenner S, Cheung AK, Liu ZH, Li J, Hooi LS, Liu W, Kadowaki T, Nangaku M, Levin A, Cherney D, Maggioni AP, Pontremoli R, Deo R, Goto S, Rossello X, Tuttle KR, Steubl D, Petrini M, Massey D, Eilbracht J, Brueckmann M, Landray MJ, Baigent C, Haynes R. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 2023; **388**: 117-127 [PMID: 36331190 DOI: 10.1056/NEJMoa2204233]

20 **Nuffield Department of Population Health Renal Studies Group**; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet* 2022; **400**: 1788-1801 [PMID: 36351458 DOI: 10.1016/S0140-6736(22)02074-8]

21 **Savarese G**, Uijl A, Lund LH, Anker SD, Asselbergs F, Fitchett D, Inzucchi SE, Koudstaal S, Ofstad AP, Schrage B, Vedin O, Wanner C, Zannad F, Zwiener I, Butler J. Empagliflozin in Heart Failure With Predicted Preserved Versus Reduced Ejection Fraction: Data From the EMPA-REG OUTCOME Trial. *J Card Fail* 2021; **27**: 888-895 [PMID: 34364665 DOI: 10.1016/j.cardfail.2021.05.012]

22 **Figtree GA**, Rådholm K, Barrett TD, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Matthews DR, Shaw W, Neal B. Effects of Canagliflozin on Heart Failure Outcomes Associated With Preserved and Reduced Ejection Fraction in Type 2 Diabetes Mellitus. *Circulation* 2019; **139**: 2591-2593 [PMID: 30882240 DOI: 10.1161/CIRCULATIONAHA.119.040057]

23 **Verma S**, McMurray JJV. The Serendipitous Story of SGLT2 Inhibitors in Heart Failure. *Circulation* 2019; **139**: 2537-2541 [PMID: 30882236 DOI: 10.1161/CIRCULATIONAHA.119.040514]

24 **Cosentino F**, Cannon CP, Cherney DZI, Masiukiewicz U, Pratley R, Dagogo-Jack S, Frederich R, Charbonnel B, Mancuso J, Shih WJ, Terra SG, Cater NB, Gantz I, McGuire DK; VERTIS CV Investigators. Efficacy of Ertugliflozin on Heart Failure-Related Events in Patients With Type 2 Diabetes Mellitus and Established Atherosclerotic Cardiovascular Disease: Results of the VERTIS CV Trial. *Circulation* 2020; **142**: 2205-2215 [PMID: 33026243 DOI: 10.1161/CIRCULATIONAHA.120.050255]

25 **Neuen BL**, Oshima M, Perkovic V, Agarwal R, Arnott C, Bakris G, Cannon CP, Charytan DM, Edwards R, Górriz JL, Jardine MJ, Levin A, Neal B, De Nicola L, Pollock C, Rosenthal N, Wheeler DC, Mahaffey KW, Heerspink HJL. Effects of canagliflozin on serum potassium in people with diabetes and chronic kidney disease: the CREDENCE trial. *Eur Heart J* 2021; **42**: 4891-4901 [PMID: 34423370 DOI: 10.1093/eurheartj/ehab497]

26 **McMurray JJV**, Wheeler DC, Stefánsson BV, Jongs N, Postmus D, Correa-Rotter R, Chertow GM, Hou FF, Rossing P, Sjöström CD, Solomon SD, Toto RD, Langkilde AM, Heerspink HJL; DAPA-CKD Trial Committees and Investigators. Effects of Dapagliflozin in Patients With Kidney Disease, With and Without Heart Failure. *JACC Heart Fail* 2021; **9**: 807-820 [PMID: 34446370 DOI: 10.1016/j.jchf.2021.06.017]

27 **Heerspink HJL**, Sjöström CD, Jongs N, Chertow GM, Kosiborod M, Hou FF, McMurray JJV, Rossing P, Correa-Rotter R, Kurlyandskaya R, Stefansson BV, Toto RD, Langkilde AM, Wheeler DC; DAPA-CKD Trial Committees and Investigators. Effects of dapagliflozin on mortality

in patients with chronic kidney disease: a pre-specified analysis from the DAPA-CKD randomized controlled trial. *Eur Heart J* 2021; **42**: 1216-1227 [PMID: 33792669 DOI: 10.1093/eurheartj/ehab094]

28 **Petrie MC**, Verma S, Docherty KF, Inzucchi SE, Anand I, Belohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett J, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Vinh PN, Schou M, Tereshchenko S, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Ponikowski P, Sabatine MS, Sjöstrand M, Solomon SD, Johanson P, Greasley PJ, Boulton D, Bengtsson O, Jhund PS, McMurray JJV. Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients With Heart Failure With and Without Diabetes. *JAMA* 2020; **323**: 1353-1368 [PMID: 32219386 DOI: 10.1001/jama.2020.1906]

29 **Desai AS**, Jhund PS, Claggett BL, Vaduganathan M, Miao ZM, Kondo T, Barkoudah E, Brahimi A, Connolly E, Finn P, Lang NN, Mc Causland FR, McGrath M, Petrie MC, McMurray JJV, Solomon SD. Effect of Dapagliflozin on Cause-Specific Mortality in Patients With Heart Failure Across the Spectrum of Ejection Fraction: A Participant-Level Pooled Analysis of DAPA-HF and DELIVER. *JAMA Cardiol* 2022; **7**: 1227-1234 [PMID: 36189985 DOI: 10.1001/jamacardio.2022.3736]

30 **Jhund PS**, Kondo T, Butt JH, Docherty KF, Claggett BL, Desai AS, Vaduganathan M, Gasparyan SB, Bengtsson O, Lindholm D, Petersson M, Langkilde AM, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Køber L, Lam CSP, Martinez FA, Sabatine MS, Shah SJ, Solomon SD, McMurray JJV. Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. *Nat Med* 2022; **28**: 1956-1964 [PMID: 36030328 DOI: 10.1038/s41591-022-01971-4]

31 **Butler J**, Packer M, Filippatos G, Ferreira JP, Zeller C, Schnee J, Brueckmann M, Pocock SJ, Zannad F, Anker SD. Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. *Eur Heart J* 2022; **43**: 416-426 [PMID: 34878502 DOI: 10.1093/eurheartj/ehab798]

32 **Verma S**, Anker SD, Butler J, Bhatt DL. Early initiation of SGLT2 inhibitors is important, irrespective of ejection fraction: SOLOIST-WHF in perspective. *ESC Heart Failure* 2020; **7**: 3261-3267 [DOI: 10.1002/ehf2.13148]

33 **Kato ET**, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RHM, Kuder J, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Bonaca MP, Ruff CT, Desai AS, Goto S, Johansson PA, Gause-Nilsson I, Johanson P, Langkilde AM, Raz I, Sabatine MS, Wiviott SD. Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. *Circulation* 2019; **139**: 2528-2536 [PMID: 30882238 DOI: 10.1161/CIRCULATIONAHA.119.040130]

34 **Bhatia K**, Jain V, Gupta K, Bansal A, Fox A, Qamar A, Damman K, Vaduganathan M. Prevention of heart failure events with sodium-glucose co-transporter 2 inhibitors across a spectrum of cardio-renal-metabolic risk. *Eur J Heart Fail* 2021; **23**: 1002-1008 [PMID: 33609071 DOI: 10.1002/ejhf.2135]

35 **Peikert A**, Chandra A, Kosiborod MN, Claggett BL, Desai AS, Jhund PS, Lam CSP, Inzucchi SE, Martinez FA, de Boer RA, Hernandez AF, Shah SJ, Janssens SP, Belohlávek J, Borleffs CJW, Dobreanu D, Langkilde AM, Bengtsson O, Petersson M, McMurray JJV, Solomon SD, Vaduganathan M. Association of Dapagliflozin vs Placebo With Individual Kansas City Cardiomyopathy Questionnaire Components in Patients With Heart Failure With Mildly Reduced or Preserved Ejection Fraction: A Secondary Analysis of the DELIVER Trial. *JAMA Cardiol* 2023; **8**: 684-690 [PMID: 37208998 DOI: 10.1001/jamacardio.2023.1342]

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