The value of clinical trials and cohort studies in nephrology

Vivekanand Jha
Go et al, N Engl J Med 2004

Age-Standardized Rate of Cardiovascular Events (per 100 person-yr)

<table>
<thead>
<tr>
<th>Estimated GFR (ml/min/1.73 m²)</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>2.11</td>
</tr>
<tr>
<td>45–59</td>
<td>3.65</td>
</tr>
<tr>
<td>30–44</td>
<td>11.29</td>
</tr>
<tr>
<td>15–29</td>
<td>21.80</td>
</tr>
<tr>
<td>&lt;15</td>
<td>36.60</td>
</tr>
</tbody>
</table>

Go et al, N Engl J Med 2004
What do we want to know?

Who is at highest risk of developing CV complications?

What interventions are safe and effective in reducing complication risk?
Evidence-based medicine pyramid

- Systematic Reviews
- Critically-Appraised Topics [Evidence Syntheses and Guidelines]
- Critically-Appraised Individual Articles [Article Synopses]
- Randomized Controlled Trials (RCTs)
- Cohort Studies
- Case-Controlled Studies / Case Series / Reports
- Background Information / Expert Opinion

Filtered Information

Unfiltered Information
Why do we need clinical trials?

• Essential to the development of new medical treatments and diagnostic tests
• Allow testing and monitoring of the effect of a treatment on a large number of people to ensure that any improvement as a result of the treatment occurs for many people and is not just a random effect
• New intervention will usually be compared against a control (placebo or an established intervention already in use)
Observational studies can get the effect of intervention wrong, usually in favor of the intervention.
Clinical trials

• Improve health care services by raising standards of treatment.

• Doctors and hospital staff involved in clinical trials are continually trained to provide best practice patient care.
New approaches to clinical trials

- Culture change
- Trial networks: bigger and better trials
- Patient engagement
- Novel trial designs:
  - Registry-based trials
  - Adaptive designs
- Standardized core outcomes

Craig et al, NDT 2017
Explanatory and pragmatic clinical trials

**Explanatory**
- Narrow
- Highly Targeted
- Single, Specialty Center
- Research Infrastructure
- Strict Protocol
- Incentives, Censoring
- Specific to Trial
- Surrogates, Biomarkers
- As-Treated

**Pragmatic**
- Eligibility
- Recruitment
- Setting
- Organization
- Delivery
- Adherence
- Follow-Up
- Outcome
- Analysis
- Broad
- In Clinic
- Usual Care
- Clinical Infrastructure
- Flexible Protocol
- Usual Encouragement
- Available Metrics
- Relevant to Patients
- Intention to Treat

de Boer et al, JASN 2016
Platform trial

Hiddo J.L. Heerspink, and Vlado Perkovic CJASN
doi:10.2215/CJN.01290118

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Generalizability of clinical trial results

- Research and those pursuing it should respect the diversity of human culture and conditions and take full account of ethnicity, gender, disability, age, and sexual orientation in its design, undertaking, and reporting. Researchers should take account of the multicultural nature of society. It is particularly important that the body of research evidence available to policy makers reflects the diversity of the population.
Using Standardized Serum Creatinine Values in the Modification of Modified Glomerular Filtration Rate Estimating Equation for Chinese Patients with Chronic Kidney Disease
Revised Equations for Estimated GFR From Serum Creatinine in Japan

Kunihiko Akizawa, Seiichi Matsuo, MD, PhD, Enyu Imai, MD, PhD, Masaru Horio, MD, PhD

A New Equation to Estimate Glomerular Filtration Rate

Andrew S. Levey, MD, PhD, Harold I. Feldman, MD, Josef Coresh, MD, PhD

Modification for Japanese Patients

Masaru Horio, MD, PhD

The need for robust validation for MDRD-based glomerular filtration rate estimation in various CKD populations

Kearkiat Praditpornsilpa, Natavudh Townamchai, Tawatchai Chaiwatanarat, Khajohn Tiranathanagul, Pisut Kawaiwat, Paweena Susantisotchong, Thananda Trakarnvanich, Talermsak Kanjanabuch, Yingyos Avihingsan, Kriang Tungsanga and Somchai Eiam-Ong
Creatinine-based estimation equations overestimate GFR in Indian population

Kumar et al, BMC Nephrol 2018
Examples...

- Anemia studies
- Dialysis adequacy studies
- Glomerulonephritis RCTs
  - IgA nephropathy
- SHARP
- PLEXIVAS
- SGLT2 inhibitors
- Complement inhibitors....
ISN-Advancing Clinical Trials (ACT)

Facilitating more high-quality clinical trials around the world through exchange, training and collaboration.

Menu
- Research
- Clinical Research Program
- H4KH Research Initiative
- iNET-CKD
- ISN-ACT
• **Aim:** to increase the number of international high-quality clinical trials in nephrology, informing the optimal prevention/treatment/ complications for the benefit of patients with kidney disease.

• **Goals**
  - To bring together people undertaking clinical trials and related studies in nephrology - facilitate interaction, experience sharing, collaboration
  - Forum for the discussion of key scientific, operational and analytic issues facing clinical trial researchers in kidney disease
  - Grow the capacity to conduct high quality clinical trials and studies by connecting researchers and through specific training initiatives

https://www.theisn.org/research/isn-act
Cohort studies

• Group of individuals with a common feature followed in time to evaluate for incident events that occur over time
• Follow-up time should be sufficient for outcomes to occur
• Can be historical or prospective
• Analyses and results should be hypothesis driven and biologically plausible
• RCTs can be converted into cohort studies
• Use non-renal outcome studies to examine renal end points
• Remain susceptible to bias and confounding

Tonelli and Thadhani cJASN 2006
Cohort studies

- Healthy people
- Exposure occurs
- Exposed & unexposed
- Disease occurs
- Diseased & non-diseased
Cohort studies

- Critical for identifying etiologic factors for disease
- Hypothesis generating for estimating intervention effects
- May be used to confirm RCT findings
- Causal inferences cannot be made about the effects of interventions
Cost determinants

- Ascertainment method
  - Registry vs. household enumeration
- Active vs. passive follow up
- How much data to collect
- Driven by the scope and goals of a given study
- Use technology (call centers, computerized instruments, sensors)
Biorepository

• Provide future value to cohort studies
• Permit measurement of biomarkers of exposures or intermediate phenotypes often not even imagined at the time the study is initiated
• Central processing –
  – increased consistency
  – achievable throughput
  – robust data trail
  – lower costs
New models of cohort studies

- Ensure collection of widest possible range of outcomes to permit combining data for increased study power
- Use standardized or harmonized (not identical but comparable) measures to permit diverse studies to be combined
- Establish consents that allow for broad data sharing as the norm
- Maximize cost-efficiency where appropriate by

http://www.datashaper.org/
Maximize cost-efficiency in cohort studies

- Centralized recruitment and examination models
- Lower recruitment yield if associations rather than prevalence are the primary objective
- Utilizing electronic records
- Industrial-scale process expertise as the driver of process organization, implementation, and monitoring
- Use IT to ensure high-quality data, rapid transfer, and real-time monitoring
- Phasing activities to be completed only shortly before they are needed
Cohort studies: centralized model

Assessment Center 1
Examine

Assessment Center 2
Examine

Assessment Center 7
Examine

Assessment Center 8
Examine

Assessment Center 6
Examine

Assessment Center 12
Examine

Assessment Center 3
Examine

Assessment Center 9
Examine

Assessment Center 5
Examine

Assessment Center 11
Examine

Assessment Center 10
Examine

Coordinating Center

Information Technology

Data Quality Control

Training, Certification

Locate: Respond
Equip: Recruit
Staff: Recontact
Supply: Ascertain
Invite: Repository

Manolio et al, Am J Epidemiol 2012
Purpose: Understanding CKD progression and its consequences can be enhanced through collaboration among investigators implementing observational research studies in CKD.

Goals:
- To promote and enhance research opportunities using patient-level data and bio-samples to understand CKD progression and outcomes
- To enhance research capacity around the world through education, especially as pertains to the conduct of observational cohort studies
- To assist investigators establish CKD cohort studies.

https://www.theisn.org/research/inet-ckd
Chronic kidney disease in Asia – Protocol for a collaborative overview

Thaminda Liyanage, Toshiharu Ninomiya, Vlado Perkovic, Mark Woodward, Heide Stirnadel-Farrant, Kunihiro Matsushita, Kunitoshi Iseki, Hooi Lai Seong, Helen Monaghan, Vivekanand Jha

Accepted manuscript online: 17 May 2016  Full publication history

DOI: 10.1111/nep.12821  View/save citation

Cited by: 0 articles  Citation tools
Prevalence of CKD in Asia

• Systematic review to identify published literature on the prevalence of CKD in Asia

• CKD risk factors from WHO Global Health Observatory data repository for Asian countries

• Life expectancy at birth, gross national income

• Eligible for inclusion: ≥500 adults (≥18 years) from Asia

• CKD prevalence estimated where data is unavailable
Figure 2: Classification of Asian countries according to the risk factors

Countries included in the same shaded area were classified as the same cluster.
### Number of patients and prevalence for all CKD and CKD stage 3-5 in East and South Asia

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Countries</th>
<th>Number of patients aged ≥20 years in 2015 (x million)</th>
<th>Number of patients (95% CI) (x million)</th>
<th>Prevalence (95% CI) (%)</th>
<th>Number of patients (95% CI) (x million)</th>
<th>Prevalence (95% CI) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All CKD</td>
<td>Prevalence</td>
<td></td>
<td>CKD stage 3-5</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Afghanistan</td>
<td>14.368</td>
<td>1.509 (0.812 to 2.206)</td>
<td>10.5 (5.7 to 15.4)</td>
<td>0.762 (0.481 to 1.042)</td>
<td>5.3 (3.4 to 7.3)</td>
</tr>
<tr>
<td></td>
<td>Bangladesh</td>
<td>97.467</td>
<td>12.476 (9.941 to 15.01)</td>
<td>12.8 (10.2 to 15.4)</td>
<td>5.848 (4.046 to 7.65)</td>
<td>6.0 (4.2 to 7.8)</td>
</tr>
<tr>
<td></td>
<td>Cambodia</td>
<td>9.082</td>
<td>0.954 (0.513 to 1.394)</td>
<td>10.5 (5.7 to 15.4)</td>
<td>0.481 (0.304 to 0.658)</td>
<td>5.3 (3.4 to 7.3)</td>
</tr>
<tr>
<td></td>
<td>India</td>
<td>810.276</td>
<td>139.367 (131.35 to 147.385)</td>
<td>17.2 (16.2 to 18.2)</td>
<td>47.806 (42.8 to 52.812)</td>
<td>5.9 (5.3 to 6.5)</td>
</tr>
<tr>
<td></td>
<td>Indonesia</td>
<td>163.301</td>
<td>12.248 (11.379 to 13.117)</td>
<td>7.5 (7.0 to 8.0)</td>
<td>8.655 (5.471 to 11.839)</td>
<td>5.3 (3.4 to 7.3)</td>
</tr>
<tr>
<td></td>
<td>Laos</td>
<td>3.684</td>
<td>0.387 (0.208 to 0.565)</td>
<td>10.5 (5.7 to 15.4)</td>
<td>0.195 (0.123 to 0.267)</td>
<td>5.3 (3.4 to 7.3)</td>
</tr>
<tr>
<td></td>
<td>Myanmar</td>
<td>34.066</td>
<td>3.577 (1.925 to 5.229)</td>
<td>10.5 (5.7 to 15.4)</td>
<td>1.805 (1.141 to 2.47)</td>
<td>5.3 (3.4 to 7.3)</td>
</tr>
<tr>
<td></td>
<td>Nepal</td>
<td>15.944</td>
<td>1.69 (1.52 to 1.86)</td>
<td>10.6 (9.5 to 11.7)</td>
<td>1.004 (0.871 to 1.138)</td>
<td>6.3 (5.5 to 7.1)</td>
</tr>
<tr>
<td></td>
<td>North Korea</td>
<td>17.878</td>
<td>1.877 (1.01 to 2.744)</td>
<td>10.5 (5.7 to 15.4)</td>
<td>0.948 (0.599 to 1.296)</td>
<td>5.3 (3.4 to 7.3)</td>
</tr>
<tr>
<td></td>
<td>Philippines</td>
<td>58.404</td>
<td>1.518 (0.38 to 2.657)</td>
<td>2.6 (0.7 to 4.6)</td>
<td>1.518 (0.38 to 2.657)</td>
<td>2.6 (0.7 to 4.6)</td>
</tr>
<tr>
<td></td>
<td>Timor-Leste</td>
<td>0.555</td>
<td>0.058 (0.031 to 0.085)</td>
<td>10.5 (5.7 to 15.4)</td>
<td>0.029 (0.019 to 0.04)</td>
<td>5.3 (3.4 to 7.3)</td>
</tr>
<tr>
<td></td>
<td>Viet Nam</td>
<td>64.898</td>
<td>1.533 (1.387 to 1.679)</td>
<td>4.7 (4.3 to 5.2)</td>
<td>1.003 (0.884 to 1.122)</td>
<td>3.1 (2.7 to 3.5)</td>
</tr>
<tr>
<td>2</td>
<td>Bhutan</td>
<td>0.493</td>
<td>0.039 (0.035 to 0.044)</td>
<td>8.0 (7.1 to 8.9)</td>
<td>0.039 (0.035 to 0.044)</td>
<td>8.0 (7.1 to 8.9)</td>
</tr>
<tr>
<td></td>
<td>Pakistan</td>
<td>103.475</td>
<td>0.003 (0.003 to 0.004)</td>
<td>8.0 (7.1 to 8.9)</td>
<td>0.003 (0.003 to 0.004)</td>
<td>8.0 (7.1 to 8.9)</td>
</tr>
<tr>
<td></td>
<td>China</td>
<td>1,060.004</td>
<td>150.225 (146.881 to 153.568)</td>
<td>14.2 (13.9 to 14.5)</td>
<td>19.063 (17.789 to 20.337)</td>
<td>1.8 (1.7 to 1.9)</td>
</tr>
<tr>
<td>3</td>
<td>Malaysia</td>
<td>20.124</td>
<td>1.825 (1.443 to 2.208)</td>
<td>9.1 (7.2 to 11.0)</td>
<td>0.563 (0.344 to 0.783)</td>
<td>2.8 (1.7 to 3.9)</td>
</tr>
<tr>
<td></td>
<td>Maldives</td>
<td>0.231</td>
<td>0.028 (0.016 to 0.039)</td>
<td>12.0 (7.1 to 16.9)</td>
<td>0.012 (0.003 to 0.02)</td>
<td>5.0 (1.4 to 8.6)</td>
</tr>
<tr>
<td></td>
<td>Sri Lanka</td>
<td>14.040</td>
<td>1.012 (0.981 to 1.042)</td>
<td>7.2 (7.0 to 7.4)</td>
<td>0.977 (0.947 to 1.007)</td>
<td>7.0 (6.7 to 7.2)</td>
</tr>
<tr>
<td></td>
<td>Thailand</td>
<td>51.521</td>
<td>9.016 (8.364 to 9.668)</td>
<td>17.5 (16.2 to 18.8)</td>
<td>4.431 (3.949 to 4.912)</td>
<td>8.6 (7.7 to 9.5)</td>
</tr>
<tr>
<td></td>
<td>Japan</td>
<td>104.341</td>
<td>13.773 (13.682 to 13.864)</td>
<td>13.2 (13.1 to 13.3)</td>
<td>11.373 (11.289 to 11.457)</td>
<td>10.9 (10.8 to 11.0)</td>
</tr>
<tr>
<td>4</td>
<td>Korea</td>
<td>39.994</td>
<td>6.939 (6.536 to 7.342)</td>
<td>17.4 (16.3 to 18.4)</td>
<td>1.524 (1.328 to 1.72)</td>
<td>3.8 (3.3 to 4.3)</td>
</tr>
<tr>
<td></td>
<td>Singapore</td>
<td>4.375</td>
<td>0.683 (0.636 to 0.729)</td>
<td>15.6 (14.5 to 16.7)</td>
<td>0.232 (0.203 to 0.261)</td>
<td>5.3 (4.6 to 6.0)</td>
</tr>
<tr>
<td></td>
<td>Brunei</td>
<td>0.290</td>
<td>0.034 (0.032 to 0.035)</td>
<td>11.6 (11.0 to 12.2)</td>
<td>0.034 (0.032 to 0.035)</td>
<td>11.6 (11.0 to 12.2)</td>
</tr>
<tr>
<td></td>
<td>Iran (b)</td>
<td>54.953</td>
<td>6.375 (6.019 to 6.73)</td>
<td>11.6 (11.0 to 12.2)</td>
<td>6.375 (6.019 to 6.73)</td>
<td>11.6 (11.0 to 12.2)</td>
</tr>
<tr>
<td>5</td>
<td>Mongolia</td>
<td>1.895</td>
<td>0.263 (0.223 to 0.304)</td>
<td>13.9 (11.8 to 16.0)</td>
<td>0.15 (0.118 to 0.181)</td>
<td>7.9 (6.2 to 9.6)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>17.526</td>
<td>2.086 (2.069 to 2.102)</td>
<td>11.9 (11.8 to 12.0)</td>
<td>1.209 (1.196 to 1.222)</td>
<td>6.9 (6.8 to 7.0)</td>
</tr>
<tr>
<td></td>
<td>Taiwan</td>
<td>116.041 (100.353 to 131.729)</td>
<td>13.4 (12.6 to 14.2)</td>
<td></td>
<td></td>
<td>4.2 (3.6 to 4.8)</td>
</tr>
</tbody>
</table>

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1. Number of patients and prevalence among subjects aged 40 years or older, because of no available data for subjects aged 20-39 years.

2. The number of patients and prevalence among subjects aged 20 years or older, because of no available data for subjects aged 40 years or older.

3. The prevalence is based on the estimated number of patients.

4. The prevalence is based on the estimated number of patients.

5. The prevalence is based on the estimated number of patients.

6. The prevalence is based on the estimated number of patients.
Conclusions

- Patients with kidney disease need better management, which will occur through more and better clinical studies.
- Recognize the need for, and complementary nature of, a variety of designs and approaches.
- Studies should be:
  - focused on information needs
  - Robust in design and reporting
  - Measure relevant outcomes
  - Use methods to increase relevance to routine care
SPECIAL FOCUS: END STAGE KIDNEY DISEASE