Editorial Comments

From Helsinki to Istanbul: What can the transplant community learn from experience in clinical research?*

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Keywords: clinical research; living donation; transplant ethics

In June of 1964, the World Medical Association developed the ‘Declaration of Helsinki’ (available at www.wma.net) as a statement of ethical principles to provide guidance to investigators and physicians involved in human research. Over 40 years later the declaration remains ‘... a respected institution and one of the most influential documents in clinical research’ [1]. Though it is not binding to any local or international law, it draws its authority from the degree to which it has been codified, or influenced, as well as from national or regional legislation and regulations. Despite criticisms, the declaration is widely accredited with improving both the ethical and scientific quality of clinical research. It should be recalled however that the Helsinki Declaration was not developed and adopted in a vacuum; it was a response to horrific abuses of human rights, in the name of scientific research and medical progress, such as those perpetrated on inmates of Nazi concentration camps.

In April of 2008, representatives of the international organ transplant community will be meeting in Istanbul to face a situation that bears comparison to that faced by clinical researchers in the 1960s. Documents designed to codify the ethical treatment of living donors have been published by professional transplantation organizations but their impact is limited [2,3]. The use, by Chinese authorities, of organs from executed prisoners [4] certainly ranks as a crime against humanity and an abrogation of basic human rights, as does the exploitation of destitute or vulnerable organ ‘donors’ by traffickers in many parts of the world. All the parties in the vigorous debate that is taking place in the lay and professional press over the wisdom of commercialization of living donation abhor these abuses. The core of the debate is how best to put an end to such abuses. As we struggle to find an answer, what can we learn from the experience of the clinical researchers? Can the international transplant community produce its own declaration that will have the authority to protect the rights of living donors while promoting healthy transplant practice?

The text of the Helsinki Declaration

The introduction to the Helsinki Declaration includes the following categorical statement taken from the International Code of Medical Ethics:

A physician shall act only in the patient’s interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient.

It also recalls that

It is the duty of the physician to protect the life, health, privacy, and dignity of the human subject.

For those of us engaged in living organ donation, this serves as a reminder that the organ donor is no less a patient than is the recipient of his or her organs. As such, the living organ donor is entitled to the same degree of advocacy that is presumed for the recipient. A favourable outcome to a living donor transplant requires that both the donor and recipient do well, both in the short-term and the long-term, and both from a strictly medical and psychosocial standpoint.

There is an ongoing need for new pharmaceutical agents to treat life-threatening illness, just as there is a shortage of organ donors for recipients with advanced organ failure. Yet, the introduction to the Declaration of Helsinki includes the following statement:

... considerations related to the well-being of the human subject should take precedence over the interests of science and society.

With this point, the Declaration is reminding us that the welfare of the research subject should be more important than the success of the project in which he or she is engaged. Similarly, the welfare of the living donor must not be sacrificed because of the needs of recipients: the ends must not be used to justify the means. A long waiting list for kidney transplants is not an adequate reason to loosen concern for the welfare of donors: in contrast, it is a cause for...
even greater vigilance, lest the threat to the long-suffering recipients become an alibi to lower the standards for donor protection.

Further, the Helsinki Declaration is cognizant of the fact that research subjects may come from populations who are vulnerable, either because of illness or because of social status:

The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required ... for those who may be subject to giving consent under duress.

The same concerns certainly apply to living organ donors in the event that they come from economically or otherwise disadvantaged populations.

In the debate over the commercialization or incentivization of kidney donation, it sometimes appears as if wide cultural, political and religious differences between countries will make it difficult to come up with a common set of guiding values. Similar challenges face clinical researchers all over the world, yet the Helsinki Declaration declares that

No national, ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this declaration.

The living organ donor, just like the human research subject, ought to have basic rights and protections that are universal. Human subjects in any part of the world should be protected by an irreducible set of ethical standards [5], so should living organ donors.

The Helsinki Declaration reminds us that

The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

The mere fact that an individual agrees to be subjected to a research protocol cannot be used as justification for its application. Consent is not a free license; research subject autonomy does not trump medical advocacy. Translated to the world of organ transplantation this reminds us that a living donor consent does not free the physicians from responsibility for his or her welfare, defined in the broadest sense.

The Declaration goes on to state that

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed.

Translated to the realm of living organ donation, consent to undergo a nephrectomy requires a nuanced understanding, by both the medical team and the donor, of the potential short- and long-term implications of the procedure. Potential living donors who may be educationally, socially or economically vulnerable to a degree that does not allow them to adequately assess risk and benefit should not be permitted to donate in any system, whether commercialized or altruistic.

Further,

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

Available evidence suggests that altruistic living organ donors, in spite of, or perhaps because of, the absence of financial gain, do indeed benefit from donation in terms of self-esteem, psychologic well-being, and social status [6]. Such benefits do not appear to accrue to commercialized donors, many of whom appear to be dissatisfied with their outcome [7] or even to suffer significant psychosocial injury [8,9].

Financial compensation for research subjects and living donors

The Helsinki Declaration is silent on the issue of financial compensation for research subjects. In the United States, Federal regulations, based on the Belmont Report—Ethical Principles for the Protection of Human subjects of Research (available at http://ohsr.od.nih.gov/guidelines/belmont.html)—require that local Institutional Review Boards (IRBs) ensure that the possibility of coercion or undue influence of prospective research subjects be minimized. Payment for research is not considered a benefit of participation, but instead a compensation for time and inconvenience. Clinical investigators must identify the amount and schedule of all payments. The IRB serves to ensure that the amount, method and timing of the reimbursement are not coercive or unduly influential. Recruitment materials for clinical research subjects should not emphasize payment or characterize it as a benefit.

But how does one estimate the dollar value of compensation? Much of the ongoing debate over the incentivization or commercialization of organ transplant donation echoes the debate that has taken place over the years over payment of research subjects. Dickert and Grady [10] have described the persistent ethical challenge that exists because of the tension between the need to recruit subjects for clinical research studies and the obligation to offer them certain types of protection. They describe advantages and disadvantages of three models of reimbursement and their application: the market model, the wage-payment model and the reimbursement model.

The market model, based on a ‘supply and demand’ philosophy that would permit the payment of large sums of money to potential research subjects, is similar in many respects to that proposed by proponents of commercialized kidney transplant donation. Not only do the authors regard this model to be ethically problematic, they make the following critical point: ‘... large total payments and completion bonuses may provide an incentive for the subject not to explore carefully the risks and benefits of the research or to conceal important health information in order to become or remain eligible for the study and thus receive payment’. Evidence suggests that the higher the payment level the greater is the propensity to conceal [11]. Parallel concerns have been addressed regarding the impact of payment of large sums of money to potential living kidney donors [12]: the propensity to conceal relevant information in these circumstances may account for the high incidence of infectious complications in recipients
of vended kidneys [13]. The provision of employment to otherwise unemployed potential living kidney donors would also be subject to the same ethical and practical limitations.

The reimbursement model for the payment of the expenses of research subjects is non-controversial in its application to living donors and is already codified by law in the United States (available at www.optn.org) and in the ethics statements of professional transplant organizations [14]. It aims to make the procedure ‘revenue neutral’ by reimbursing expenses required for travel, parking, child care, meals, lodging, phone calls and time away from work. In this respect, federal law in the United States currently permits paid leave for 1 month for government employees (Public Law 1999; 24: 106–56) and many private employers have similar programs (list available at www.a-s-t.org). The reimbursement model is intended to preclude financial profit for the research subject and the living donor. Though currently not typically included, the provision of health insurance for living donation-related medical problems, short-term life insurance and expenses for supporting family members is also consistent with the reimbursement model [15]. It should be noted that the reimbursement model takes no account of the effort or discomfort involved either in research or organ donation.

The wage-payment model operates on the principle that participation in a research project requires little skill on the part of the research subject but may require time, effort and endurance of undesirable or uncomfortable procedures. Subjects are paid on a scale that is commensurate with other unskilled but essential jobs [10]. This model can be used to assess the financial value of the time lost from work in the reimbursement model so as to avoid wide variation among subjects with different earning potential. Application of some combination of the reimbursement model and the wage-payment model has been recommended and has typically led to the payment to research subjects of small amounts of money, by Western standards [16]. Application of the wage-payment model to living donors for a finite period until they return to work might be consistent with the principles of the Helsinki Declaration in countries where employment rates are high and social disparity is limited. Such payments could be individualized up to a fixed ceiling and reviewed by a standing committee to ensure probity. In countries with high unemployment rates and wide social disparities, even the relatively small amount of money resulting from the application of the wage-payment model could lead to the exploitation of vulnerable populations in a manner inconsistent with the intent of the Declaration. The vulnerable, in countries both rich and poor, with high and low unemployment rates, and developed and undeveloped social ‘safety-nets’, are not appropriate candidates for living organ donation.

Next steps

How can the international transplant community replicate or advance the role of the Helsinki Declaration in protecting research subjects and raise the standard of the global transplant endeavour? How can a new declaration succeed when other well-meaning efforts have not? The Helsinki Declaration has succeeded, despite not being established in international law, because of the recognition that the whole field of clinical research and its critical benefits for mankind were gravely threatened by egregious abuse. National supervisory bodies and IRBs will not approve clinical research protocols unless they ascribe to the Helsinki Declaration; pharmaceutical companies will not permit their nascent products to be clinically tested unless the protections of the Helsinki Declaration are in place, and medical journals will not publish the results of clinical research unless it is categorically stated that the rights of the research subjects have been protected. Similarly it is appropriate to require that governmental accreditation of organ transplant programs include proof of protection for living organ donors; that insurance coverage for living donor transplant procedures be conditioned on such protection; that national and international transplant databases insist on such protection as a condition of inclusion; that membership in professional societies be restricted to those who accept such conditions; and that presentation or publication of clinical research involving living donors be similarly conditioned.

It is naïve to presume that the application by the transplant community of these and similar measures would bring to an end the criminal and unethical exploitation of living donors that cast such a long shadow. The Helsinki Declaration did not end the abuse of clinical research subjects but it has certainly improved their lot. With disciplined application of similar principles, the integrity of international transplant endeavour can be maintained and strengthened, not just for the welfare of living donors, but for the welfare of patients with end-stage organ failure all over the world: it is they who have the most to gain from healthy organ transplant practice.

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Fact or fiction of the epidemic of chronic kidney disease—let us not squabble about estimated GFR only, but also focus on albuminuria

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Keywords: albuminuria; chronic kidney disease; glomerular filtration rate; proteinuria; screening

Introduction

In this issue of the journal, Glassock and Winearls question the need to conclude that there is an epidemic of chronic kidney disease (CKD) [1], while Coresh et al. emphasize in their response that there definitely is a need to study glomerular filtration rate (GFR) estimates [2]. This is an important debate since after the publication of the KDOQI guidelines on the classification of CKD in 2002, many programs have been started to screen subjects for CKD, in an attempt towards preventing complications in the subjects involved. In this respect, it is important to note that CKD is not only associated with an enhanced risk of developing ESRD, but also with an increased risk of cardiovascular events [3].

The definition of the five stages of chronic kidney disease

The detection of subjects with CKD is facilitated by clear definitions on what we should screen for and who we should screen. For this purpose, the KDOQI classification has a great value. This classification is based upon two manifestations of renal damage: first, the presence of either micro- and macro-albuminuria, erythrocyturia or abnormalities on renal ultrasound and second, an impaired eGFR [4]. In fact, an impaired eGFR is the only characteristic needed to define a subject as having a stage 3, 4 or 5 CKD (eGFR 30–59, 15–29 or <15 ml/min/1.73 m², respectively). The presence of other signs of renal damage is not required for the definition of stages 3–5. These are mandatory for the definition of the stage 1 and 2 CKD, while measurement of the eGFR in these earlier stages is required only to distinguish between stages 1 and 2 (increased albuminuria, erythrocyturia or abnormal ultrasound, together with the eGFR >90 or 60–89 ml/min/1.73 m², respectively).

For assessing renal damage besides an impaired eGFR, most surveys use a well-defined measure of micro-albuminuria [5–8] or dipstick-positive proteinuria [9–11]. A dipstick test is easy to apply and cheap. Many patients with dipstick positivity appear to have micro-albuminuria during confirmation. Of the subjects that were trace, 1+ or 2+ positive on a protein dipstick, 61, 71 and 41% had micro-albuminuria, whereas only 1, 7 and 50% had macro-albuminuria, thus showing that the submaximal categories of dipstick positivity are more indicative of micro- than macro-albuminuria [12]. However, these data also show that dipsticks are often false positive, limiting their applicability for screening purposes. In this respect, it seems more prudent for population screening to use a quantitative and more accurate measurement of urinary albumin by nephelometry in a laboratory or a point-of-care device [13].
The risks associated with elevated albuminuria and impaired GFR

Interestingly, micro-albuminuria, similar to an impaired GFR, has been found to be associated with an increased risk for cardiovascular events [14,15]. This risk is independent of the risk induced by an impaired GFR [8,10]. In this respect, it is disappointing that both papers on the pro-con debate in this journal only focus on the impact of a correct eGFR measurement for the definition of CKD, thus limiting the discussion to CKD stages 3–5 [1,2]. Remarkably, in the paper by Coresh et al., the importance of micro-albuminuria or proteinuria in the CKD definition is acknowledged only by arguing that papers are being published on this topic [2]. They then refer to two papers that are in press in late 2007 or early 2008, but do not discuss the numerous papers that have been published on this topic in the last decade and have recently been reviewed [16]. The pro-con debate, as it now stands, thus mainly discusses the pros and cons of taking care of stage 3 CKD patients. It is emphasized by Glassock and Winearls that the female to male ratio of stage 3 patients is 1.75:1, while the opposite is seen in treated ESRD (0.6:1), suggesting that the definition of stage 3 patients is not appropriate [1]. It has also been shown that most of the patients with an impaired GFR have fairly stable renal function during follow-up [17]. It is thus not unexpected that Glassock and Winearls question whether we should redefine stage 3 CKD. They propose a lower cut-off value that Glassock and Winearls question whether we should redefine stage 3 CKD. They propose a lower cut-off value

The renal and cardiovascular risk of stages 1 and 2 versus that of stage 3

Unfortunately, the debate on the epidemic of CKD limits itself to the better definition of stage 3 subjects. The attention that this debate gets entails the danger that we forget to pay attention to stage 1 and 2 CKD patients; the patients with signs of renal damage, but with still normal or only modestly impaired eGFR. As we lack an optimal measure for renal function in this higher eGFR range, it is questionable whether there is a real need to know exactly whether a subject has CKD stage 1 or 2. It has been shown that the incidence rate of a new CV event was equally increased in stage 1 and 2 CKD patients (21 per 1000 person years) and stage 3 CKD patients (21 per 1000 person years), compared to the normal population (7 per 1000 person years). The same held true for developing a renal event (defined as need for renal replacement therapy): 0.5 per 1000 person years in stage 1 and 2 and 0.8 in stage 3 CKD compared to 0.02 in the normal population [19]. Some studies evaluated the risks of elevated albuminuria and impaired GFR separately. Both in a study in subjects with pre-existing coronary heart disease [10] as in a general population cohort [8], the risk of developing a CV event is higher in stage 1 and 2 subjects (GFR > 60, but micro- and macro-albuminuria positive) than in subjects without CKD (GFR > 60, Alb−) (Figure 1). Interestingly, however, the risk was not increased in subjects with stage 3 CKD without increased albuminuria (GFR < 60, Alb−). Only in stage 3 CKD subjects with albuminuria (GFR < 60, Alb+) was the CV risk elevated (see Figure 1) [8,10]. In the MRfit study it was similarly shown that the risk of developing a renal event (the need to start renal replacement therapy) was elevated ∼12-fold in stage 1 and 2 subjects with micro-albuminuria as compared to subjects with no CKD (Figure 2), while the risk was only increased 2.4-fold in stage 3 subjects who did not have micro-albuminuria. The increase was most pronounced in stage 3 subjects with micro-albuminuria: 33-fold [11].

Screening only for an impaired GFR or also for elevated albuminuria?

These data emphasize that it is prudent to look not only for the level of an eGFR, but at least as important, also for the presence of micro- or macro-albuminuria. We recently discussed the differences in approach to screen for CKD in various parts of the world [19]. Some favour targeted screening, that is, a screening of specific groups such as
subjects with known diabetes or with hypertension, or the elderly. This option has been argued to be more cost-effective [20,21]. This, however, is dependent on the expected number of diabetic and hypertensive subjects in a population, which is different in various parts of the world. Moreover, we should realize that for every subject with known hypertension or diabetes, there is one subject in the population in which this diagnosis has not yet been made, but who can have already considerable associated end-organ damage [22,23]. It has even been shown that the presence of micro-albuminuria may even precede the diagnosis of hypertension [24] and diabetes [25]. Finally, subjects with known diabetes or hypertension frequently are already instituted on renoprotective and cardioprotective regimens. Lastly, it is important to realize that when we focus screening on these target groups, we most likely will have to screen 50% of the population.

Another approach has been advocated in the UK [17,26,27]. These studies used centralized laboratory databases to select subjects with an eGFR <60 ml/min/1.73 m². This database approach offers the advantage that we may limit the screening especially to those with a repeated measure of an impaired eGFR, to be sure it is a chronic problem. Another advantage of this approach is that one may limit more precise measurements of CV and renal risk factors to the less than ∼5% of the population that has an impaired GFR. However, disadvantages of such screening on known eGFR values in databases have been extensively discussed in the paper by Glassock and Winearls [1]. Moreover, as argued above, by not screening for albuminuria we will overlook all patients with stage 1 and 2 CKD, who are at greater risk than subjects in stage 3 without micro- and macroalbuminuria.

Since there are far more subjects with elevated albuminuria than with a seriously impaired eGFR, and since most subjects with a seriously impaired eGFR have also increased albuminuria, we advocate an approach of first screening for the presence of elevated albuminuria. That can be done by a simple dipstick test as described above [9,12], with the limitation of low specificity. In the PREVEND study a more specific approach was tested. The entire adult population of the city of Groningen was invited to send by post a vial containing a sample of the first morning urine void to a central laboratory facility for precise albumin measurement by nephelometry. In this way, information on the urinary albumin concentration and albumin creatinine ratio was obtained from about half of the population [28]. The procedure of sending urine vials by post is less expensive than drawing blood for screening on an eGFR in a large number of subjects. All subjects with a urinary albumin concentration >10 mg/l were next invited for confirmation of increased albumin excretion and further evaluation of renal and CV risk factors. This approach, followed by a 4-year treatment with an ACE inhibitor in those who were found to be micro-albuminuric, was shown to be cost-effective in preventing CV events [29].

Conclusions

Though the KDOQI classification of CKD in stages gave an enormous impetus to the screening of CKD, the pro-con debate in this issue of the journal shows that there is presently an increasing unwillingness to diagnose the many subjects with stage 3 CKD as being at risk, especially since most do not show progressive renal nor cardiovascular disease. We agree that there is need to improve the definitions of stage 3 CKD. We favour doing so by including the presence of kidney damage as manifested from an elevated albuminuria in stage 3. We, moreover, want to emphasize that the stage 1 and 2 patients with elevated albuminuria, but with a (fairly) normal eGFR, have a worse prognosis than the present stage 3 patients without elevated albuminuria. We therefore suggest focussing the screening practice also on the measurement of albuminuria, instead of looking only for an impaired eGFR.

Conflict of interest statement. None declared.


(See related article by Josef Coresh et al. Chronic kidney disease is common: What do we do next? Nephrol Dial Transplant 2008; 23: 1122–1125.)

References

Tubulointerstitial nephritis and uveitis syndrome (TINU): a step forward to understanding an elusive oculorenal syndrome

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Keywords: TINU syndrome; differential diagnosis TINU syndrome; pathogenesis TINU syndrome

In this issue of NDT, Sartelet et al. [1] provide an interesting study on Tubulointerstitial Nephritis and Uveitis syndrome (TINU), an oculorenal syndrome the pathophysiology of which is still poorly understood.

TINU is a rare disease, first described in 1975 by Dobrin [2] in two adolescent girls, in whom non-caseating granulomas were found in the bone marrow and in the lymph nodes, in association with anterior uveitis and tubulointerstitial nephritis. Since then, more than 200 cases have been
Toxoplasmosis Nephrotic syndrome, haemolytic–uraemic syndrome, Toxocariasis Mesangioproliferative glomerulonephritis Leukocoria, red eye, uveitis, heterochromia, vitritis, vasculitis, Tuberculosis Cystitis, calyceal distortion, ureteric strictures and bladder.

Table 1. Differential diagnosis for the TINU syndrome [7,8]

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Renal manifestations</th>
<th>Ocular manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus</td>
<td>Proteinuria, haematuria, nephrotic or nephrotic syndrome, renal insufficiency, hypertension, lupus glomerulonephritis</td>
<td>Retinal vasculitis, dysoric retinopathy, retinal haemorrhage, anterior uveitis, papilloedema, optic neuropathy, cranial nerve palsies or central nervous system vasculitis, cortical blindness</td>
</tr>
<tr>
<td>Guogerot-Sjögren</td>
<td>Tubulointerstitial nephritis, tubulopathy, hypercalcaemia, nephrocalcinosis, nephrogenic diabetes insipidus, renal insufficiency, immune complex glomerulonephritis</td>
<td>Sclera syndrome</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Tubulointerstitial nephritis ± granuloma, hypercalcaemia, renal calculi, nephrocalcinosis, renal insufficiency membranous nephropathy, proliferative or crescentic glomerulonephritis, focal glomerulosclerosis</td>
<td>Anterior and posterior uveitis, optic neuropathy retinal peripheplebitis, macular oedema, renal neovascularization, granuloma formation in the retina, choroid, optic nerve or lacrimal gland, secondary glaucoma, cataract formation</td>
</tr>
<tr>
<td>Rhumatoid arthritis</td>
<td>Renal vasculitis, AA renal amyloidosis</td>
<td>Scleritis, sicca syndrome</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td>Pauciimmune crescentic glomerulonephritis, renal insufficiency, genitourinary aneurysms, papillary necrosis, ureteral and prostatic involvement, retroperitoneal fibrosis</td>
<td>Orbital inflammatory pseudotumor, scleritis, episcleritis, conjunctivitis, peripheral ulcerative keratitis, uveitis, optic neuritis, retinal artery occlusion, cranial nerve palsies and proptosis, conjunctival ulceration</td>
</tr>
<tr>
<td>Behçet’s disease</td>
<td>Renal AA amyloidosis, proliferative glomerulonephritis, necrotizing vasculitis</td>
<td>Non-granulomatous anterior uveitis, retinal vasculitis, vascular occlusion and optic neuritis, neovascularization, paralytic strabismus, vitreous hemorrhage, secondary cataracts and glaucoma</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Cystitis, calyceal distortion, ureteric strictures and bladder fibrosis, calcified and non-functioning kidney, tubulointerstitial nephritis with granuloma formation and caseation, AA amyloidosis, nephrothiasis</td>
<td>Scleral perforation, keratoconjunctivitis, chronic and diffuse iridocyclitis, papillary sclebritis, secondary glaucoma, chronic diffuse choroiditis, retinal peripheplebitis and neovascularization, retinal detachment, optic nerve involvement, orbital tuberculosis</td>
</tr>
<tr>
<td>Toxocariasis</td>
<td>Mesangio proliferative glomerulonephritis</td>
<td>Leukocoria, red eye, uveitis, heterochromia, vitritis, vasculitis, peripheral granuloma and retinal detachment, strabismus</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Nephrotic syndrome, haemolytic–uraemic syndrome, glomerulonephritis, interstitial nephritis</td>
<td>Granulomatous uveitis, Fuchs heterochronic cyclitis, recurrent retinochoroiditis, retinal vasculitis, vascular occlusion, serous retinal detachment, vitritis, optic neuropathy</td>
</tr>
<tr>
<td>TINU syndrome</td>
<td>Tubulointerstitial nephritis</td>
<td>Anterior uveitis, posterior synechiae, cataract and elevated intraocular pressure</td>
</tr>
</tbody>
</table>

The differential diagnosis for interstitial nephritis associated with uveitis is broad (Table 1). Further ocular findings, in addition to those that characterize uveitis, help suggest the correct diagnosis in these cases [7,8]. Sarcoidosis and Sjögren’s syndrome expression is close to that of TINU, making an accurate diagnosis difficult in the absence of a specific involvement of other organs.

The pathophysiology of TINU is still unknown. Renal tubular and ciliary body epithelia share several functions, including those pertaining to electrolyte transporters sensitive to carbonic anhydrase inhibitors. It is conceivable that they share closely related antigens that account for a cross-reactivity. Specific basement membrane antigens have been found to be immunogenic in animal models of acute interstitial nephritis, and some patients with acute interstitial nephritis express antibodies to the tubular basement membranes (TBMs) [4]. Immunofluorescence using sera from patients with anti-TBM nephritis revealed their localization in the TBMs of the proximal and, to a lesser extent, the distal tubule and Bowman’s capsule, and also the basal membrane of the intestinal mucosa [9,10]. Although rare, human anti-TBM nephritis has been reported in some cases related to drugs [11], in transplanted patients [12]; some cases occur in the absence of any detectable underlying disease [13]. Only few patients with TINU were specifically reported to have immunofluorescent TBM staining indicating antibody deposition [14,15].

Sartelet et al. [1] report for the first time the presence of autoantibodies recognizing a common antigen found in
tubular and uveal cells, in the serum of a 15-year-old girl suffering from TINU. After a negative standard direct immunofluorescence, the serum of the patient and that of a normal healthy human control were deposited on frozen sections of the normal human kidney and normal mouse eye. Immunofluorescence microscopy showed focal cytoplasmic IgG deposits on proximal and distal tubular epithelial cells along with membranous IgG deposits in uveal cells (ciliary body and iris) incubated with the patient’s serum. There were no IgA or IgM deposits and no deposits in sections incubated with a normal serum. This forms an original set of findings in TINU.

However, the presence of autoantibodies does not necessarily indicate the presence of an autoimmune disease. As an example, natural anti-glomerular basement membrane autoantibodies exist in normal human sera [16]. More information is therefore required to establish the causative role of the antibodies observed by Sartelet et al. Nevertheless, the identification of circulating antibodies against uveal proteins, even when their precise nature has not been elucidated, incites to attribute an autoimmune background to the patient’s illness. The unique case presented by Sartelet et al. is of particular interest in that it adduces arguments for a pathophysiologic role of concomitant anti-uveal and anti-renal tubule antibodies.

The experience to date indicates that continued search for, and identification of, anti-TBM antibodies, in the renal tissue and in the serum of patients with TINU syndrome, is warranted. In this respect, Sartelet et al.’s case provides a strong incentive to pursue this quest with renewed conviction.

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Periodic paralyses: when channels go wrong

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Keywords: channel; hyperkalaemia; hypokalaemia; transcellular shift

In 1865, Claude Bernard wrote that ‘the constancy of the internal milieu is the essential condition to a free and independent life’ [1]. It would be hard to find a more illustrative paradigm for that statement than for the case of hyperkalaemic periodic paralysis (HyperPP) reported by Grgic et al. in this issue [2]. A 14-year-old male was admitted for a sudden ascending paralysis involving the four limbs that appeared shortly after exercise. The symptoms were associated with a severe hyperkalaemia (6.3 mmol/L). Remarkably, both the muscle strength and the K+ level normalized spontaneously within 2 h. Since the patient had presented similar episodes since childhood, a clinical diagnosis of HyperPP was made, later confirmed by provocation with exercise and oral K+ intake. Genetic analysis detected a known mutation (T704M) in the SCN4A α-subunit of the Nav1.4 voltage-gated sodium channel. The mutation was not detected in the biological parents of the proband. This case is relevant for K+ homeostasis, Na+ channelopathies and genotype–phenotype correlations.

Potassium homeostasis

Potassium is the most abundant cation in the human body, with total body stores amounting to 50 mmol/kg in adults. Less than 2% of K+ is located extracellularly, and kalaemia is maintained in the narrow range of 3.5–5.0 mmol/L. The compartmentalization of K+ inside cells is critical for maintaining cell volume, DNA and protein synthesis, and regulating intracellular pH, enzymatic activities and cell growth. Normal individuals ingesting 80–100 mmol of K+ daily remain in balance by virtue of short-term transcellular K+ shifts regulated by insulin, aldosterone and β-adrenergic catecholamines (β2 receptors), which increase the cellular K+ uptake by stimulating the sodium pump (Na+/K+-ATPase), and the excretion of 90% of the ingested K+ in the urine and the remaining in stool. Since the resting membrane potential primarily depends on the steep transmembrane K+ gradient, variations in kalaemia influence the excitability of neuromuscular tissues including the heart and the skeletal muscles [3].

Hyperkalaemia and K+ redistribution

Hyperkalaemia is a relatively common and potentially life-threatening condition. If we exclude pseudohyperkalaemia, in which K+ exits cells during or after blood sampling, three main mechanisms lead to hyperkalaemia: (i) excess intake; (ii) impaired renal excretion and (iii) redistribution (or transcellular shift) of K+ between intracellular and extracellular fluid compartments, too fast to be corrected by renal excretion. Conditions that are associated with variations of the transmembrane K+ ratio include severe muscle activity; tissue injury; inorganic metabolic acidosis; increased extracellular osmolality; drugs interfering with insulin, catecholamines or aldosterone; the use of succinylcholine, a myorelaxant that depolarizes the cell membrane; and digitalis intoxication, which inhibits the Na+/K+-ATPase [4]. HyperPP is another example of the transcellular shift of K+ out of the cells, due to mutations in specific voltage-gated sodium channels (Na,K,Chs) in skeletal muscle cells.

The periodic paralyses, paradigm for muscle channelopathies

The periodic paralyses are rare and dominantly inherited disorders characterized by neuromuscular symptoms (paralysis and myotonia) associated with marked and transitory variations of K+ levels in the plasma [5,6] (Table 1). Symptoms usually appear during the first or second decade of life and can be life-threatening if heart or respiratory muscles are involved. The paralysis corresponds to muscular flaccidity (paraplegia or tetraplegia) with reversible hypo/excitability of the cells. Myotonia is defined by a delayed relaxation of tensed muscles following a powerful contraction, due to sarcolemmal hyperexcitability [7]. Except for very rare normokalaemic cases [8], periodic paralyses are usually classified by the changes in kalaemia during the crisis: hypokalaemic periodic paralysis (HypopPP) and hyperkalaemic periodic paralysis (HyperPP). These two entities show distinct clinical features. Paralysis expression is constant, whereas myotonia is found only in HyperPP. In general, HyperPP attacks occur in the morning and resolve shortly, whereas HypoPP starts during night, with symptoms lasting up to one day. Triggering factors also differ: K+ can provoke HyperPP attacks, whereas carbohydrate-rich or Na+-rich meals trigger HypoPP. Cold, emotions, fasting or rest after exercise may also trigger HyperPP crisis. The typical history and transient course of the attacks often suggest the diagnosis, which can be confirmed by...
mutation analysis (see below). Provocative tests (K+ intake or exercise) are useful in some cases but should be performed with caution. The first treatment for both types of PP is to avoid triggering factors and to normalize plasma K+ levels. Carbonic anhydrase inhibitors and diuretics are used to prevent the attacks [5,6].

HyperPP is caused by mutations in the SCN4A gene that encodes the α subunit of the Na\textsubscript{v} Ch Na\textsubscript{1.4} in skeletal muscles [9–11]. Na\textsubscript{v} Chs are pore-forming membrane proteins mediating Na\textsuperscript{+} influx involved in the initiation and transmission of action potentials in excitable tissues such as muscles, heart and nerves [12]. These channels are gated by changes in the membrane potential, switching between the closed, activated and inactivated states according to membrane potential variations (Figure 1A). The activation of Na\textsubscript{v} Chs by membrane depolarization causes Na\textsuperscript{+} influx responsible for the sudden membrane depolarization in the initial phase of the action potential. In response, there is a compensatory outward K+ current that perpetuates the process along the membrane. The fast inactivation (within milliseconds) of Na\textsubscript{v} Chs is essential for membrane repolarization [12].

Like all members of the Na\textsubscript{v} Chs family, Na\textsubscript{v} 1.4 is made up of a principal pore-forming α subunit, associated with an accessory β subunit. The α subunit consists of four domains, each comprising six transmembrane segments which form the ion-selective pore and confer the voltage dependence of the protein, whereas the intracellular loop between the domains III and IV is involved in the inactivation process (Figure 1B). SCN4A was an early candidate gene for PP, since in vitro studies demonstrated an abnormal Na\textsuperscript{+} conductance in the muscle cell membrane [13]. Linkage analysis [9] and demonstration of missense mutations [10,11] confirmed that SCN4A was responsible for HyperPP. Since then, eight missense mutations of SCN4A have been identified in HyperPP (Figure 1B). The T704M mutation described by Grgic et al. [2] was first reported in 1991 [10]. Reminiscent of the case discussed here, the mutation cosegregated with HyperPP in two families, but appeared as de novo in the third one [10]. The T704M mutation is detected in half the families with HyperPP, whereas the M1592V mutation accounts for one-third of cases [5,12]. Of interest, phenotype variability due to the T704M mutation has been documented in a family with paralysis periodicum paramyotonia [14].

### From mutations to disease

Most of the SCN4A mutations causing HyperPP are located in the inner part of transmembrane segments or in the intracellular loops (Figure 1B), where they affect the fast inactivation of the channel [15–17]. As compared to wild-type channels, mutant channels show incomplete inactivation resulting in an increased level of persistent Na\textsuperscript{+} current (gain of function) that causes a sustained membrane depolarization [18]. In turn, the sustained depolarization will favour K+ release from the cells, causing hyperkalaemia, and inactivate the majority of Na\textsubscript{v} Chs, causing electrical inexcitability of skeletal muscles [6,12].

Mutations in SCN4A are not only detected in HyperPP, but also in a minority of patients with HypoPP (HypoPP type 2) and normokalaemic PP in paramyotonia congenita, potassium-aggravated myotonia and congenital myasthenia [5,19]. Such diversity raises the issue of genotype–phenotype correlations. At variance with the gain of function mutations of SCN4A causing HyperPP, the majority of mutations associated with HypoPP are located in the voltage-sensing transmembrane S4 segment of the domain II of Na\textsubscript{v} 1.4 (Figure 1B), resulting in a stabilization of the closed state of the channel (loss of function) [20]. However, recent studies demonstrated that HypoPP mutations of arginine residues within the domain II create a cation leakage that is not caused by a defect of the
HyperPP is a typical example of transcellular shifts of \( K^+ \) caused by mutations in skeletal muscle \( Na^+ \) channels. The attacks of HyperPP impact on the daily life of young patients, causing familial and social problems [6]. The episodic nature of the disease, with normal muscle function in between, may complicate the diagnosis. Electrophysiological studies and provocative tests can be useful, although caution should be taken with the latter. Advances in the molecular genetics of channelopathies facilitate the diagnosis, since two mutations of \( SCN4A \) account for the majority of HyperPP cases. With more cases documented, genotype–phenotype correlations are emerging, which are essential to decipher the pathophysiology of the diseases caused by Na\(^+\)_Chs mutations. Insights into the structure of these channels should lead to the development of compounds that would provide more specific therapies.

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(See related article by I. Gragic et al. Hyperkalaemia in a tetraplegic adolescent due to \textit{de novo} sodium channel mutation. \textit{Nephrol Dial Transplant} 2008; 23: 1449–1451.)

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Renal tubular acidosis (RTA) is an uncommon disorder; however, the subgroup of isolated familial proximal RTA (pRTA) is exceedingly rare. The term ‘isolated’ pRTA distinguishes these disorders from Fanconi syndrome, in which proximal tubular transport proteins are impaired as well. In this issue of Nephrology Dialysis Transplantation, Katzir et al. [1] report findings in a single family with a specific form of isolated familial pRTA. It is highly likely that only very few physicians will ever encounter a case of this nature in their professional lives. Why then would this report be of interest?

The human body generates ~50–100 mmol of mineral acid per day. This load must be excreted, to prevent metabolic acidosis. Cells function best at physiologic pH; hence it is advantageous for the body to keep pH as constant as possible. The kidney is the only organ equipped to fully excrete the daily acid load, and the proximal tubule is the workhorse of that process. It transports hydrogen ion into the tubular lumen, reabsorbs bicarbonate (Figure 1) and contributes to the excretion of ammonium (NH₄⁺) and titratable acid. The machinery consists of a number of integrated tools (Figure 1): a Na⁺/H⁺ exchanger and Na⁺-K⁺-ATPase; a Na⁺/HCO₃⁻ co-transporter in the basolateral membrane (kNBC-1) to facilitate translocation of bicarbonate to the extracellular fluid; carbonic anhydrases II and IV, which function in the disposition of CO₂ (Figure 1).

In the era of molecular biology, how does this model hold up? Are there inherited mutations of the transport proteins that confirm the model? This is indeed in part what was found. ‘Autosomal recessive pRTA with ocular abnormalities’ is, for instance, attributable to homozygous mutations in the gene for kNBC-1 (Figure 1) [2]. Affected patients show pRTA and short stature, glaucoma and cataracts, psychomotor delay and calcification of basal ganglia and bone. A Met-to-Val mutation in the sodium channel α-subunit gene is associated with the autosomal recessive form of pRTA [2].

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Proximal RTA: Are all the charts completed yet?

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hyperamylasaemia. In addition to its expression in the renal proximal tubule, NBC-1 is also present in the epithelia of eye, brain and pancreas, which is likely to explain the diverse findings.

‘Sporadic isolated pRTA’ is a non-familial, transient pRTA observed in early childhood. Affected individuals present with pRTA, short stature and vomiting. Alkali therapy is helpful and the disorder disappears after a few years [3]. It is held that continued immaturity of NBC-1 beyond the neonatal period is involved but disappears later in life.

‘Autosomal dominant pRTA’ is a disorder of pRTA and short stature but no other abnormalities. It has thus far been described only once in nine members of a single family [4] over 20 years ago. Because of the kidney specific distribution of NHE-3 and based on a knock-out model of NHE-3 in mice [5], it was predicted that mutations of NHE-3 would be found, explaining autosomal dominant pRTA. However, the report by Katzir et al., in this issue of NDT, casts doubt on that proposal.

Katzir et al. [1] describe only the second family in the literature with autosomal dominant pRTA. The affected individuals had a pH in blood of 7.13, bicarbonate of 13.9 mmol/L, hyperchloreaemia and a low urinary pH of 5.4. An oral bicarbonate loading test partially corrected the metabolic acidosis, the urinary pH increased to 6.8 and the fractional excretion of bicarbonate rose to 22%. The findings were therefore the characteristic of pRTA. However, sequencing of genomic DNA from the patient and four affected family members failed to uncover mutations of NHE-3 and its regulatory proteins NHRF1 and NHRF2, nor were any mutations of other candidate genes (Figure 1) found.

What are the implications of these unexpected results? Is the technique or the concept at fault? The authors amplified and sequenced the coding areas and splice sites of the genes of interest. They also performed a haplotype analysis of introns and regulatory sequences of the candidate genes, using three to four microsatellite markers in each gene. If the reconstructed haplotypes were dissimilar between affected individuals, they were excluded as potential causes of the phenotypic defect. A lot of analysis must have been involved in this work; however, there may still be a possibility that three to four microsatellite markers are not sufficient to fully study the introns and the promoter area of a gene, or to exclude small changes such as a point mutation. It is notoriously difficult to completely exclude technical difficulty; we shall not know this with any certainty until more clusters of patients are studied.

What if our concept of obligatory proteins in pRTA (Figure 1) was deficient? Could there be transporters in pRTA that have been overlooked? The authors consider that a new enzyme or a regulatory factor related to the trafficking of NHE-3 might be involved. Indeed in the present work, the authors were unable to fully exclude the regulatory protein of NHE-3 NHRF1 from being involved. Given the limited phenotype of autosomal dominant pRTA and the kidney-specific distribution of NHE-3, they might conceivably be correct. Alternatively is it possible that a luminal H\(^{+}\)-ATPase has a role in the human proximal tubule? In the rat it was shown that an apical vacuolar H\(^{+}\)-ATPase contributed about one-third to bicarbonate reclamation in that segment [6]. Still other experiments in the salamander suggested the presence of tertiary active hydrogen ion secretion in the proximal tubule [7]. This mechanism utilizes an apical Na\(^{+}\)-lactate and a basolateral membrane H\(^{+}\)-lactate cotransporter. Finally bicarbonate has a paracellular backleak pathway into the tubular fluid in the late proximal tubule of the rat [8]. Could it become leakier than physiological and thus contribute to pRTA in humans?

Taken together, the inability of Katzir et al. to explain clear-cut pRTA in their patients on the basis of known transport mechanisms brings up the question as to whether other mechanisms could be involved and what they are. It will be exciting to see how this enigma unravels in the future.

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Pharmacoeconomics in nephrology: considerations on cost-effectiveness of screening for albuminuria

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Introduction

In this issue, Palmer et al. [1] demonstrate that screening for nephropathy in hypertensive type 2 diabetic patients and subsequent treatment with renoprotective antihypertensive agents may result in excellent value for money from the US health care perspective. Estimated costs and effects were combined in a cost-utility analysis, to express the incremental costs per quality-adjusted life year (QALY) for add-on treatment of the angiotensin receptor blocker (ARB) irbesartan after detection of nephropathy through screening, compared with conventional antihypertensive treatment only, in the absence of screening. Nephropathy was defined as microalbuminuria or nephropathy; i.e. urine albumin excretion (UAE) >20 μg/min (corresponding to a UAE expressed per 24 h > 30 mg/24 h, with >300 mg/24 h generally defining nephropathy). Such screening and subsequent ARB treatment—add on to conventional antihypertensive therapy—was estimated to result in favourable clinical outcomes with only marginally increasing overall costs. Furthermore, estimated incremental cost-effectiveness was well below a willingness to pay (WTP) threshold of US$50 000 per QALY for the USA [2]. Despite the fact that such an absolute quantitative threshold for costs per QALY has to be interpreted with caution by decision-makers in health care systems, the exact cost-per-QALY ratio found by the authors at US$20 011 per QALY gained and an estimated 77% probability of being below this US$50 000 threshold certainly suggest a favourable pharmacoeconomic profile [1,3]. Palmer et al. used a Markov model to simulate the progression from a healthy state to end-stage renal diseases (ESRDs) and second-order Monte Carlo simulation—both ‘state-of-the-art’ mathematical techniques in pharmacoeconomics—to account for multiple parameter uncertainty and to derive results as listed above [3,4]. In this editorial, we discuss the results as listed above [3,4]. In this editorial, we discuss the study by Palmer et al. from the viewpoint of pharmacoeconomic science.

How to conduct a pharmacoeconomic analysis?

Pharmacoeconomics is defined as the science focusing on scarcity of budgets for pharmacotherapeutic interventions; i.e. that part of health economics with the focus on pharmacotherapy. Cost-effectiveness and cost-utility analysis are the main instruments used in pharmacoeconomics. Cost-effectiveness analyses relate differences between monetary costs and benefits (net costs) of an intervention to a clinical outcome, such as blood-pressure lowering, serious events avoided or life-years gained. In cost-utility analyses, net costs of an intervention are related to gains in quality of life and life years gained (including the quality of those years), both expressed and aggregated in QALYs [3]. As such, a QALY integrates gains in survival and gains in quality during life. For the reimbursement of new drugs—such as ARBs in the last decade—currently in many countries pharmacoeconomic research is required and the outcome of it should indicate that a new drug is ‘cost-effective’ (i.e. below a certain predefined, or thought, threshold for net costs per outcome considered, usually life-year gained or QALY gained). Examples in nephrology in recent years exist next to ARBs: for example, are sorafenib and sunitinib cost-effective enough in the treatment of renal cell carcinoma to justify their reimbursement?

Also, such pharmacoeconomic analyses should adhere to guidelines for the conduct of such studies, guaranteeing a minimum quality level. These guidelines are globally rather uniform and some of them warrant some remarks here. Firstly, full economic evaluations should ideally be performed from the societal perspective. The societal perspective typically includes indirect non-medical costs of production losses, next to direct medical costs [5]. Secondly, these analyses should include all short- and long-term costs and effects. Ideally, a lifelong perspective is applied. Therefore, long-term analyses are now required to support drug reimbursement decisions or implementation of large-scale interventions, such as screening or vaccination programs. Despite sophisticated methods developed and used for economic analyses on short-term clinical studies, such analyses are often considered to be insufficient,
given the lack of a long-term perspective. Thirdly, long-term perspectives—beyond clinical-trial horizons—require the use of adequate modelling techniques, such as Markov models. Markov models generally enable the analysis of transitions from one health state (for example, microalbuminuria) to another (for example, nephropathy), within a framework of a predefined number of such health states. In the model, quality of life is generally defined per state; durations of stay in these states can easily be analysed over long time frames.

Palmer et al. [1] developed a Markov model to simulate disease progression over a 25-year time frame approximating a lifetime perspective, even more so, as a discount rate at 3% for money and health gains was applied, following US-guidelines. In pharmacoeconomic analysis, costs, savings and health gains are discounted to account for time preference; i.e. one prefers to receive an amount of money now rather than receiving that same amount of money in the future, or one prefers to pay costs in the future over paying the same amount now (a similar reasoning is assumed for health). So, pharmaco economists attach different values or utilities to amounts of money or life years that occur on different moments/periods in time: the higher the discount rate, the lower the value that is attached to costs, benefits and health gains that occur in the (distant) future. Recent discussions have focused on the appropriateness of using similar discount rates for money and health, for example with regard to discounting life years [6]. Following that discussion, the Netherlands recently changed its pharmaco economic guideline on discounting to differential discounting: 4% for money and 1.5% for health. Generally, differential discounting—i.e. relatively low discounting of health compared with money—favours preventive interventions with health gains in the (distant) future, inclusive screening programs such as those on albuminuria.

Cost-effectiveness of RAAS-intervening agents in type 2 diabetic patients

We recently reviewed within-trial analytical and Markov-model based economic evaluations of Renin Angiotensin Aldosterone System (RAAS)-intervening agents in type 2 diabetic patients [7], including those studies used by Palmer et al. [1]: RENAAL, IDNT, IRMA-2 and BENEDICT [8–11]. Economic outcomes from these studies generally suggest that treatment with RAAS-intervening agents in type 2 diabetic patients, with overt or incipient nephropathy, confers health gains and net cost-savings compared with conventional (non-RAAS) treatment [7,12]. In particular, delay of renal disease may confer relevant cost-savings in terms of ESRD, dialyses and kidney transplantations averted. Additionally, it has been shown that benefits can be expected in reducing cardiovascular events [7].

Favourable pharmaco economic outcomes for treatment may justify screening, to identify those who may benefit from such treatment. Thus, Palmer et al. [1] argue that screening for albuminuria in the specific population of hypertensive type 2 diabetic patients and subsequent start of renoprotective ARB treatment in those found positive will result in excellent value for money. It is still difficult to definitely assess the relative therapeutic values of ARBs in relation to ACE inhibitors. Indications exist to show that ACE-inhibitor treatment results in similar beneficial effects on renal disease progression and occurrence of cardiovascular events as ARBs, both in type 2 diabetic patients as well as in non-diabetic patients [11,13,14]. Except for the DETAIL-trial, however, there are no nephrological studies comparing the effectiveness of ACE inhibitors and ARBs on a head-to-head basis for specific nephrological endpoints [14]. Indirect comparison of both classes of drugs is also difficult. Most trials with ACE inhibitors are partially placebo-controlled, often with, as a result, better blood pressure control in the ACE inhibitor groups, whereas most ARB trials showed comparable blood pressure control in the experimental and control groups [7,13]. Indirect comparisons are therefore likely to favour ACE-inhibitors over ARBs.

One study simulated cost-effectiveness of universal ACE-inhibitor treatment for type 2 diabetic patients—irrespective of both blood pressure and albuminuria levels—and found this to be highly cost-effective [15]. So, beyond discussions on screening for albuminuria in type 2 diabetic patients, universal treatment of such patients with RAAS-intervening agents is already under consideration. On the one hand, this will save screening costs, and on the other hand drug costs will increase, which is particularly relevant if drugs are used prior to patent expiry. Obviously, the topic warrants further pharmaco economic analysis, including exploring the impact of price reductions as the first ACE inhibitors are now becoming off-patent, enhancing the economic profile of these agents.

Cost-effectiveness of screening in the general population

Economic evaluation based on the outcomes of the IDNT study in combination with the IRMA-2 study previously showed that ARB-treatment results in higher cost-savings if applied in the early stage of microalbuminuria compared with late overt diabetic nephropathy, both in US and European settings [16]. This suggests that the earlier the treatment is started, the better it is for hypertensive type 2 diabetic patients. Would this also apply for the non-diabetic population with albuminuria? Should we screen for microalbuminuria (UAE > 30 mg/24 h) and/or nephropathy (UAE > 300 mg/24 h) in this population as well, and would this be cost-effective? The PREVEND (Prevention of Renal and Vascular ENd stage Disease) study, as well as other studies, showed that microalbuminuria (UAE > 30 mg/24 h) presents an independent risk-factor for renal disease and cardiovascular events, also in the non-diabetic population [17]. As long as all effects in terms of renal and cardiovascular outcomes and proper cost estimates are considered, there are certainly indications that albuminuria-based ‘test-and-treat’ strategies could be a successful tool, resulting in a reduced number of renal and cardiovascular outcomes and possibly a favourable cost-effectiveness [18–20].
Boulware et al. [18] estimated that annual screening for dipstick proteinuria by general practitioners may be cost-effective to prevent ESRD in the US setting, except if limited to only elderly or hypertensive persons. However, large groups of normotensive and non-elderly groups remain, with net costs per QALY estimates that are generally considered not cost-effective. Previously, however, we argued that several rather study-specific factors determine these negative results [19]. In particular, (i) the general practitioner setting may be unnecessarily expensive and much cheaper screening might be achieved if subjects are requested to send a first morning void urine sample by post to a central laboratory, as done in the PREVEND study, or using other potentially efficient ways such as dipstick self-tests; (ii) the yield of the screening might be relevantly increased if instead of only proteinuric, microalbuminuric persons are also treated and (iii) inclusion of beneficial effects of RAAS treatment on cardiovascular events—next to ESRD—will relevantly enhance cost-effectiveness.

As a part of the observational PREVEND-study, a randomized clinical trial was undertaken (PREVEND-IT: Prevention of Renal and Vascular ENSstage Disease Intervention Trial), in which fosinopril treatment was shown to result in a statistically significant reduction in albuminuria and a strong trend towards significant difference in cardiovascular outcomes in a non-diabetic, albuminuric and primarily normotensive population [20]. The PREVEND-IT economic evaluation indicated a favourable cost-effectiveness of screening for high–normal albuminuria (UAE > 15 mg/24 h) and subsequent treatment with the ACE inhibitor fosinopril to prevent cardiovascular events [20]. This indicates that—next to screening in specific patient populations, such as hypertensive type 2 diabetic patients—screening of the general population for albuminuria could be a cost-effective strategy. Such a strategy is beneficial to prevent cardiovascular events in (micro)albuminuric persons, whereas it may be expected to prevent ESRD especially in macroalbuminuric persons. Thus, nephrological profit in albuminuria levels and ESRD is obtained in the slipstream of cardiovascular disease prevention.

Conclusion

In conclusion, favourable economic profiles in treatment of type 2 diabetic patients with nephropathy were found for ARBs. This favourable profile justifies screening for nephropathy and subsequent ARB treatment. As early treatment (starting in the stage of microalbuminuria) was found to be economically superior to late treatment (starting in the stage of overt nephropathy), a strong case exists for screening for albuminuria in diabetic type 2 patients and subsequent treatment. Possibly, this effect might be extrapolated to ACE inhibitors. In fact, for ACE inhibitors, universal treatment of all type 2 diabetic patients has even been suggested as cost-effective. For a decision on whether to prefer ARBs or ACE inhibitors, head-to-head trials are needed or at least sound indirect comparisons—comparing the effectiveness of both types of agents with non-RAAS-intervening agents at similar blood pressure control.

Further research is needed to explore the benefits of screening for albuminuria in the non-diabetic general population, and the corresponding economic profile of such a screening. For example, results on favourable cost-effectiveness from the Dutch PREVEND study require confirmation in other settings. Next to renal disease, it is important to include benefits of screening and treatment on cardiovascular events in such cost-effectiveness analyses.

Conflict of interest statement. None declared.


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