was detected. In the four cases with vein stenosis that underwent angioplasty the fistulas still failed to develop adequately. One patient had a complete occlusion of the subclavian vein. In two patients the fistulogram did not reveal any anatomic abnormality.

Finally, notwithstanding the theoretical concerns about developing hand ischemia with an upper arm fistula, only one of the 51 consecutive patients in our study receiving such a fistula developed a clinically significant steal syndrome. Thirty-one of the patients receiving an upper arm fistula were diabetic.

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REFERENCES

Dipyridamole and low-dose warfarin without cyclophosphamide in the management of IgA nephropathy

To the Editor: We were most interested to read the recent Kidney International article on evidence-based recommendations in the management of IgA nephropathy by Nolin and Courteau [1]. Recommendation 2 (grade A) states that treatment with cyclophosphamide, dipyridamole, and warfarin should not be used. This is based on the results from two randomized controlled trials (RCT), our own three-year study [2], and that of Walker et al [3], as well as our five-year post-trial assessment [4], concern about the absence of post-treatment biopsy data, and the potential toxicity from cyclophosphamide.

The authors correctly state that we were able to demonstrate reduction in proteinuria and stabilization in renal function at the end of the three-year trial. However, the apparent loss of benefit on renal function at the five-year post-trial assessment has been misinterpreted and needs to be qualified. Only half the patients in the treatment group remained on treatment with dipyridamole and low-dose warfarin at five years, which may have accounted for the failure to show significant difference in renal function compared to the control group. Nonetheless, the degree of proteinuria was significantly less in the treatment arm. The main finding from this five-year assessment, however, was that patients who stopped treatment had significantly worse renal function and were more likely (6 of 14) to progress to end-stage renal disease (ESRD) compared to those who continued treatment (0 of 13).

Clearly, this finding may be criticized for selection bias, since patients who opted to continue treatment may be more compliant and other confounding factors will influence any analysis made with the RCT as we had originally cautioned. This also applies to the interpretation made by Nolin and Courteau that the benefit seen at the end of our RCT was not sustained at five years for the reasons outlined. It should be noted that renal biopsy data in relation to the patients included in our RCT has in fact been published [5], and did reveal significantly less histologic progression among patients in the treatment group.

We would concur with the authors that cyclophosphamide is no longer justified in the management of IgA nephropathy because of its toxicity. It is because of our clinical observations, the findings of the five-year assessment, as well as the experimental evidence of a renoprotective role of dipyridamole and warfarin through immune, anti-platelet and anti-thrombotic mechanisms that we proceeded to a RCT using this regimen [6]. This three-year trial included 21 patients with IgA nephropathy and mild renal impairment, 10 patients assigned to treatment with dipyridamole and low-dose warfarin (keeping the thrombotest between 30 and 50%), and 11 patients to the control group on no treatment. At the end of the trial, renal function remained stable in patients on treatment while a significant deterioration was seen in the control group. This study suggests that treatment of patients with IgA nephropathy and renal impairment with dipyridamole and low-dose warfarin retards the deterioration in renal function.

Walker et al showed reduction in proteinuria over a two-year period but, unlike our original study using the same triple regimen and the subsequent trial without cyclophosphamide, failed to show any beneficial effect on renal function [3]. The reasons for this difference may be related to the shorter duration of treatment (2 years vs. 3 years) and the use of warfarin at the higher “anti-coagulant doses” (keeping thrombotest between 7 and 15%).

Currently there is no therapy that will cure IgA nephropathy. It is the most common form of glomerulonephritis worldwide, and is especially frequent in the East among the Chinese and Japanese and an important cause of ESRD. While we agree with Nolin and Courteau that
cyclophosphamide cannot be recommended, we suggest that there is available evidence to support the use of dipyridamole and low-dose warfarin. This regimen has been shown to be safe and its use as long-term therapy in patients with IgA nephropathy with poor prognostic indices can slow the rate of decline in renal function and progression to ESRD.

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REFERENCES

Reply from the authors

To the Editor: Drs. Woo, Lee, and Pall correctly assumed that the study “Three-year randomized controlled trial of dipyridamole and low-dose warfarin in patients with IgA nephropathy and renal impairment” (Nephrology 3:117–121, 1997) was not included in the literature we reviewed because it was published after the period covered by our Medline research (1976 through December 1996).

Their study can be classified as level 1 evidence and therefore could support a grade A recommendation for the treatment of IgA nephropathy (IgAN). However, we are concerned by the small number of patients involved in this study. Future trials hopefully will clarify the appropriate evidence-based recommendation for dipyridamole and warfarin use in IgAN treatment.

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Detection of fragments of \( \beta_2 \)-microglobulin in amyloid fibrils

To the Editor: A major controversy regarding dialysis related amyloidosis (DRA) is about the presence and the role of truncated forms of \( \beta_2 \)-microglobulin (\( \beta_2 \)M) in the amyloid fibrils. Whereas Linke et al have reported the presence of proteolyzed forms of \( \beta_2 \)M in the amyloid deposits in over 12 cases [1], other groups have not confirmed this finding [2]. A similar analysis conducted in our laboratory with \( \beta_2 \) fibrils obtained from six patients (Table 1) confirms Linke’s data.

A careful review of methods used in our and other laboratories suggests that the above-mentioned discrepancy can have two possible explanations.

The first may be the fibrils’ origin. In fact, the yield in the derivatized N-terminal residues is higher with preparations obtained from periarticular amyloid deposits of femur head in which the amyloid material is particularly abundant (Table 1). In these cases it is probably easier to detect the minor truncated species of \( \beta_2 \)M.

The second problem relates to the purification steps preceding the structural analysis. We have recently noted that \( \beta_2 \)M fragments in comparison to the complete \( \beta_2 \)M have a higher tendency to self aggregate and precipitate in non-denaturing aqueous buffers [3]. In one study in which the fragments were not detected, the purification of \( \beta_2 \)M was accomplished by chromatofocusing in non-denaturing conditions in which the loss of fragments can be expected. We think that the use of a protein sequenator like the HP G1000, in use in our laboratory, where it is possible to analyze samples in GdnHCl without further handling, could avoid the loss of even pmoles of misfolded \( \beta_2 \)M fragments.

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