# Table of Contents

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COMMENTARY

# Life expectancy in hemophilia outcome

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Ask most long-time hemophilia treaters and they will say that the development of factor concentrates has both lengthened life expectancy for people with hemophilia and improved their quality of life. Moreover, most will also say that comprehensive care has played a substantial role in these achievements. The 'In Focus' article by Plug *et al.* [1] in this issue of the journal challenges some of these beliefs. In their survey of 967 Dutch males with hemophilia from 1992–2001, which includes 8868 patient-years of follow-up (8.6 years per patient), they identified 94 deaths, roughly twice the number than in the previous two cohorts (1973–86 and 1986–92) and more than double the expected number of deaths compared with the unaffected Dutch population (39 deaths expected). The average age at death was 52 years with a wide range (14–83 years). The standard mortality ratio (SMR) was 2.3 for the group in total and 5.1 for those with severe hemophilia. Despite these observations, life expectancy of hemophilia patients has remained mostly unchanged – 67 vs. 66 and 68 years and in patients with severe disease decreasing from 63 to 59 years (Table 1). Given what we consider to be major advances in hemophilia treatment and care over the past 2 decades, these numbers, on the surface, are depressing. A closer look, however, underscores something else we already know – the decimating effect of HIV and HCV disease on the hemophilia population. Twenty-four deaths or 26% of deaths from 1992–2001 were HIV-related; 21 deaths or 22% were hepatitis C-related. As both viruses are transmitted by factor concentrate, it stands to reason that individuals with severe hemophilia would be impacted more than those with mild disease. However, if one excludes individuals with HIV and HCV disease, the SMR improves to 1.2 and general life expectancy for individuals with hemophilia approaches that of Dutch males in general – 74 years, when compared with 76 years. For those with severe disease, the SMR was 1.4 and the life expectancy 71 years. Twenty-seven percent of the deaths in the current cohort of patients not infected with HCV or HIV were because of hemorrhage (13/49) in contrast to 47% in the 1973–86 cohort [2].

An increase in the mortality rate and reduced life expectancy have been a characteristic of hemophilia as the disease was first recognized. As early as 1855, Grandidier reported an 80% mortality rate with a life expectancy of 14 years for severe and moderate cases [3]. From 1900 to 1942, the life expectancy among severe hemophilia patients in Sweden was 16.5 years in contrast to 29 years for those with mild disease [4]. The first report on the use of plasma for replacement therapy in 1923 [5] resulted in an increase in the life expectancy of patients. Between 1943 and 1957, patients with severe disease lived to 23.2 years and for those with mild disease to 50 years [3]. A similar trend was observed in USA [6]. Ikkala *et al.* [7] analyzed the data of 163 patients with severe hemophilia A living in Finland in 1930–79. During the 50 years of observation, the mean age at death increased from 7.8 years in 1930–39 to 25.5 years in 1970–79. In Sweden, between 1957 and 1980, the median age at death increased from 19 to 50 years in cases of severe hemophilia [8]. In contrast, during this time period, the life expectancy for Swedish men was 75 years. The cause of death in 56% of cases was because of various forms of hemorrhage including one-third of cases because of intracranial hemorrhage but 36% of deaths were unrelated to hemophilia (i.e. non-bleeding death). Among the patients with severe hemophilia A ($n = 30$), the incidence of inhibitory antibodies was 16.7% and 4.2% for the entire group [6]. Trauma contributed to bleeding in 23% of deaths between 1957 and 1968 but only 7% during the 12 year interval from 1969–1980. Spontaneous bleeding accounted for 42% and 41% of deaths, respectively.

Currently, children with hemophilia look forward to a normal life expectancy and excellent health-related quality of life [9]. Among 935 Dutch hemophilia patients, their view of the quality of their own health did not differ from the general Dutch population [10]. Importantly, although severity of hemophilia, arthropathy and age increased the risk of disability, home treatment was associated with a 50% reduction in this risk.

The two major factors impacting upon the improved quality of life, reduced morbidity and increased life expectancy are: (i)

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**Table 1** Hemophilia patient outcomes in the 21st century

| Cohort | Years | SMR | Life expectancy | | |
|---|---|---|---|---|---|
| | | | All patients | Severe disease | Unaffected males |
| Dutch I | 1972–1985 | 1.6 | 66 | 63 | 71 |
| Dutch II | 1985–1992 | 2.1 | 68 | 61 | 74 |
| Dutch III | 1992–2001 | 2.0 | 67 | 59 | 76 |
| HIV negative | 1992–2001 | 1.7 | 70 | 70 | 76 |
| HIV−/HCV− | 1992–2001 | 1.4 | 74 | 71 | 76 |
| Ramgren [3] | 1900–1942 | – | 16.5 | – | – |
| Ramgren [3] | 1943–1957 | – | – | 23.2 | – |
| Larsson [7] | 1930–1955 | – | – | 19 | 75 |
| Larsson [7] | 1956–1980 | – | – | 50 | 75 |

SMR, standard mortality ratio.

the availability of high-quality antihemophilic factor concentrates (AHFC) for replacement therapy and (ii) comprehensive care. Arthropathy is the major cause of morbidity in hemophilia. In the report of the Orthopaedic Outcome Study Group [11], prophylaxis significantly reduced the rate at which joints deteriorate both on physical and radiographic examination. Patients on prophylaxis had significantly fewer days lost from work or school, as well as fewer days spent in hospital. Therefore, AHFC not only reduces the likelihood of death from hemorrhage, but also offers patients the opportunity to participate in activities previously not available to those with hemophilia improving quality of life. The impact of comprehensive care is demonstrated by Soucie *et al.* [12] who reported that hemophilia patients who had received care in an HTC had a significantly decreased risk of death (relative risk and *P*-value, 0.6 and 0.002, respectively). The impact of comprehensive care is further exemplified by the analysis of 164 patients at the International Haemophilia Training Centre, Bangkok treated with blood and blood components from 1971 to 2000, in which the estimated probability of a survival beyond 13 years of age among patients with severe hemophilia increased from 0.85 during the first decade of observation to 0.94 and 1 in the second and third decades, respectively [13]. The death rate fell from 30% to 14% and 5% over the 3 decades of observation. Despite the lack of high quality AHFC for treatment, patient outcome improved with the development of a comprehensive approach to management.

As healthcare dollars become even more limited, what can we learn in terms of the care of individuals with hemophilia?

1 Firstly, the most significant impact on mortality has been from viral diseases transmitted by concentrate. Although current products appear safe from HIV and hepatitis transmission, the HIV epidemic caught us unaware. By all available data, because of the very long asymptomatic period, hepatitis C deaths will continue to increase. What about other viruses? What about prion disease? If we have learned nothing else from the AIDS epidemic, we should have learned that there is no such thing as 'completely safe' blood products. To this end, we must encourage drug manufacturers to continue working on concentrates that are completely free of animal and human proteins. Manufacturers and regulatory agencies must be encouraged to report any suspicious instances of new blood-borne pathogens to HTC physicians and patients. Finally, third party payers must not be allowed to make treatment choices for patients and physicians, choices based too often on current cost without regard for potential long-term safety.
2 Secondly, we all recognize high titer inhibitors can be difficult to control and life-threatening hemorrhage in these patients remains a reality. The incidence of inhibitors in the Dutch cohort was 50% or 5% of the total cohort, but 20% in deceased patients, suggesting the presence of an inhibitor might have contributed to the death of some patients. Still, it behooves the medical community to continue to explore more efficacious means of both treating-bleeding episodes in inhibitor patients and eradicating inhibitors. Close monitoring of patients for the appearance of an inhibitor as well as close supervision once one has been detected and during and after treatment is essential, if we are to lessen the morbidity and mortality associated with inhibitors. This requires knowledge on the part of the treating physician far beyond the expertise of most hematologists, let alone most primary care physicians. It is also very labor intensive. Given not only the medical, but also the psychological and financial ramifications involved, care of inhibitor patients is best undertaken by a team of trained healthcare providers such as seen at comprehensive care clinics.
3 Thirdly, what, if any, are the implications for comprehensive care? The authors make the point that the rate of death of people with hemophilia did not change over the years. Even worse, the rate of death of people with severe hemophilia, usually the ones most involved with comprehensive care, actually increased 4.5 times during the 1992–2001 interval when compared with 1973–86. Would we be better off putting our healthcare dollars somewhere other than toward the maintenance of comprehensive care centers? We contend not. The data presented by Plug *et al.* are heavily squewed by the deaths caused by HIV and hepatitis C and, as such, reflect specifically factor concentrate administration prior to 1986, not comprehensive care. If one looks at the life expectancy of people with hemophilia without HIV or HCV disease, it has increased to 74 years and is only 2 years shorter than that of all Dutch males. For people with severe hemophilia, it is 71 years. These numbers compare favorably to a life expectancy of 66 years, (63 years for people with severe hemophilia) in the pre-HIV/HCV days. Assuming this improvement probably has something to do with the system of care these patients are receiving, it is our opinion that we should support rather than condemn comprehensive care at this point. We feel additional studies are needed that address the specific reasons for death apart from viral infection in individuals with hemophilia. This will enable us to more specifically target those areas where additional resources are needed, while continuing to

provide client-oriented, coordinated and multidisciplinary care. This approach has probably contributed to the increased life expectancy of HIV/HCV-negative individuals with hemophilia reported by Plug *et al.*

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