Hereditary hemochromatosis (HH) is a relatively common autosomal recessive disorder of iron regulation that results in iron overload and its deposition in multiple organs. Complications include liver cirrhosis and hepatocellular carcinoma (HCC), as well as wide-ranging extrahepatic manifestations including diabetes, cardiovascular disease, arthritis, hypogonadism, and osteoporosis (Fig. 1).\(^1\)

Despite significant advances in our understanding of iron regulation, the treatment of iron-overload conditions has remained relatively static and is largely founded on historical convention. Phlebotomy remains the mainstay of treatment for HH, even in the absence of robust data from randomized trials, and although other options such as iron chelation and erythrocytapheresis are used in a minority, the ideal treatment modality and regimen remains unclear.

A lack of high-quality trial design has restricted our understanding of the clinical outcomes of iron reduction therapy, and the present data are conflicting and discordant. This absence of robust data was highlighted by a recent Cochrane meta-analysis, which attempted to collate evidence on the benefits and harms of iron reduction therapy in HH but found only two papers with usable data, precluding any consequential conclusions from being drawn.\(^2\)

Our narrative review aims to address this deficiency in the literature, with the recognition that a systematic review or meta-analysis is not currently feasible to perform, given the dearth of high-quality evidence. The numerous multisystem effects of iron reduction therapy in HH are outlined, citing the best available evidence where possible.

**Materials and Methods**

The study protocol was registered on the PROSPERO international prospective register of systematic reviews\(^3\) and carried out in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines. MEDLINE and EMBASE were searched, studies screened, and data extracted and summarized in the PRISMA diagram (Table 1 and Fig. 2).

Data were extracted by two authors independently (A.P. and T.C.) into a standardized proforma. We recorded information on the nature of the study (study
design, region where study was performed), participant demographics (age, percent male, hemochromatosis diagnosis), iron reduction therapy regimens, and clinical outcomes on mortality, cirrhosis, liver fibrosis, portal hypertension, HCC, liver transplant, arthritis, joint replacement, diabetes, cardiovascular disease, heart failure, erectile dysfunction, hypogonadism, quality of life, fatigue, biochemical iron indices, and liver function tests (Table 2).

**QUALITY ASSESSMENT OF INCLUDED STUDIES**

Two authors independently assessed the risk of bias in the included studies (A.P. and T.C.). The ROBINS-I tool⁴ or the Cochrane risk of bias tool⁵ were used to evaluate the nonrandomized and randomized studies, respectively. Disagreements were resolved by discussion, and a consensus decision was made.

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**FIG. 1.** Organs affected by HH. The hepatic and extrahepatic complications of HH are multisystemic and wide-ranging.
Results

COHORT CHARACTERISTICS

Of the 64 studies identified by the search, 24 studies from between 1972 and 2018 were included in the final cohort (5,994 patients in total) (Table 2). The remaining studies were excluded due to reporting on fewer than 20 participants (n = 15), duplication (n = 5), lack of outcome data (n = 15), inclusion of non-hemochromatosis patients (n = 4), and having not yet been performed (n = 1). One included abstract was

Note: We searched EMBASE (Ovid) (1974 to May 2018) and MEDLINE (Ovid) (1946 to May 2018) on April 4, 2018. Articles from 1950 onward were included, and there were no language restrictions. The 2,023 records were initially returned and subsequently screened.
### TABLE 2. Included Studies and Their Reported Outcomes (Marked as “Y”)

| Paper                        | No. | Mortality | Cirrhosis | HCC | Diabetes | Cardiovascular Disease | Adverse Events | Quality of Life | Fatigue | Arthralgia | ED | Biochemical Markers |
|------------------------------|-----|-----------|-----------|-----|----------|------------------------|----------------|-----------------|----------|-------------|----|---------------------|
| Dymock et al. 1972           | 115 | ..        | ..        | Y   | ..       | ..                     | ..             | ..              | ..       | ..          | .. | ..                  |
| Darnis 1972                  | 30  | Y         | ..        | ..  | Y        | ..                     | ..             | ..              | ..       | Y           | Y  | ..                  |
| Niederau et al. 1985         | 163 | Y         | Y         | Y   | Y        | ..                     | ..             | ..              | Y        | Y           | Y  | ..                  |
| Conte et al. 1986            | 67  | Y         | ..        | Y   | Y        | ..                     | ..             | ..              | Y        | ..          | .. | ..                  |
| Adams et al. 1991            | 85  | Y         | Y         | Y   | Y        | ..                     | ..             | ..              | ..       | Y           | Y  | ..                  |
| Fracanzani et al. 1995       | 120 | Y         | Y         | ..  | ..       | ..                     | ..             | ..              | ..       | ..          | .. | ..                  |
| McDonnell et al. 1999        | 2,851| ..       | ..        | ..  | ..       | Y                      | ..             | ..              | Y        | Y           | Y  | ..                  |
| Milman et al. 2001           | 158 | Y         | Y         | ..  | Y        | ..                     | ..             | ..              | Y        | ..          | .. | Y                  |
| Fatle et al. 2006            | 36  | ..        | Y         | ..  | ..       | ..                     | ..             | ..              | ..       | ..          | .. | ..                  |
| Phatak et al. 2010           | 49  | ..        | ..        | ..  | ..       | Y                      | ..             | ..              | ..       | ..          | .. | ..                  |
| Hardy et al. 2011            | 203 | ..        | ..        | ..  | ..       | ..                     | ..             | ..              | ..       | Y           | .. | ..                  |
| Brissot et al. 2011          | 210 | ..        | ..        | ..  | ..       | ..                     | ..             | ..              | ..       | ..          | .. | ..                  |
| Reháček et al. 2012          | 22  | ..        | ..        | ..  | ..       | ..                     | ..             | ..              | ..       | ..          | .. | ..                  |
| Rombout-Sestienkova et al. 2012| 38  | ..       | ..        | ..  | ..       | ..                     | ..             | ..              | ..       | ..          | .. | Y                  |
| Parra Salinas et al. 2012    | 39  | ..        | ..        | ..  | ..       | Y                      | Y              | ..              | ..       | ..          | .. | Y                  |
| Lučić et al. 2013            | 29  | ..        | ..        | ..  | ..       | ..                     | ..             | ..              | ..       | ..          | .. | Y                  |
| Sundic et al. 2014           | 62  | ..        | ..        | ..  | ..       | ..                     | ..             | ..              | ..       | ..          | .. | Y                  |
| Bardou-Jacquet et al. 2015   | 1,085| Y        | Y         | ..  | Y        | ..                     | ..             | ..              | ..       | ..          | .. | Y                  |
| Koutsovili et al. 2016       | 167 | ..        | ..        | ..  | ..       | ..                     | ..             | ..              | ..       | Y           | .. | ..                  |
| Brückl et al. 2017           | 20  | ..        | ..        | ..  | ..       | ..                     | ..             | ..              | ..       | ..          | .. | ..                  |
| Ong et al. 2017              | 104 | Y         | ..        | ..  | ..       | Y                      | Y              | Y               | Y        | Y           | Y  | ..                  |
| Chayamupatkul et al. 2017    | 196 | ..        | ..        | Y   | ..       | ..                     | ..             | ..              | ..       | ..          | .. | ..                  |
| Jabbour et al. 2018          | 39  | Y         | ..        | ..  | ..       | ..                     | ..             | ..              | ..       | ..          | .. | ..                  |
| Bardou-Jacquet et al. 2019   | 106 | Y         | Y         | ..  | ..       | ..                     | ..             | ..              | ..       | ..          | .. | ..                  |

Note: Included studies and their reported outcomes (marked as “Y”).
subsequently published as a full article in 2019; therefore, the comprehensive version was included in our analysis.

Most of the studies (n = 20, 83%) were retrospective cohort studies, whereas three (13%) were randomized controlled trials (RCTs) and one (4%) was a nonrandomized trial. The published data were skewed toward reports from Western countries, with 16 papers from Western Europe (67%), five from North America (21%), two from Eastern Europe (10%), and one from Australasia (4%).

The mean age of individuals, recorded in 14 studies, was 51 years (95% confidence interval [CI] 48-53 years old), and the mean percentage of male participants, recorded in 18 studies, was 70% (confidence interval 64%-76%). Fifteen studies (63%, 5,197 participants) included patients with HH (either confirmed by genotyping or unspecified), four studies (17%, 383 participants) included those with HH with fibrosis or cirrhosis, and five studies (21%, 420 participants) included those with HH and deranged iron indices.

The study intervention was venesection/phlebotomy in 18 studies (75%, 5,737 participants), erythrocytapheresis in four studies (17%, 185 participants), iron chelation in one study (4%, 49 participants), and phlebotomy and erythrocytapheresis in one study (4%, 49 participants).

QUALITY OF EVIDENCE

The quality-of-evidence assessments for the included studies are given in Table 3. Of the three RCTs, one was judged to be of good quality, one of fair quality, and one of poor quality. Of the 21 nonrandomized studies of intervention, 19 (90%) had a serious risk of bias, and two studies had a moderate risk. None of the included studies had a low risk of bias.

MORTALITY

Our knowledge of the natural history of HH has been derived from a retrospective follow-up of longitudinal cohorts, and survival has been found to be the same as the general population, provided that treatment is initiated in time. In our search, seven reported on mortality in patients with HH (n = 1,708, mean age 50.2 years, mean follow-up of 7.7 years (range 0-31). (7-13) All included patients were diagnosed as having primary HH on clinical grounds, with five of the seven studies predating HH genotyping, but were heterogeneous with respect to exact venesection procedure as well as to the presence of HH complications.

Crude mean overall survival was 63.7% (SD = 30.1) (four studies, n = 436, mean follow-up of 7.5 years, range 0-31 years), (7,10,12,13) and cumulative survival after follow-up was reported to be between 61% and 92% at 5 years, 61% and 81% at 10 years, and 49% and 71% at 20 years (three studies, n = 315). (7,9,13) Even in the absence of controlled trials, there is some evidence that survival of patients with HH has improved over time, coinciding with iron depletion therapy becoming the cornerstone of HH treatment. One study of patients with HH diagnosed between 1948 and 1985 found that the standardized mortality ratio (SMR) was significantly raised at 3.68 (3.07-4.39). The study also found that 10-year cumulative survival had increased within this time period (38% if diagnosed between 1948 and 1968 vs. 48% between 1969

TABLE 3. Quality of Evidence of Included Studies

| Paper                        | Quality Assessment Tool | Risk of Bias/ Assessment |
|------------------------------|-------------------------|--------------------------|
| Dymock et al. 1972           | Robins-I                | Serious                  |
| Darnis 1972                  | Robins-I                | Serious                  |
| Niederau et al. 1985         | Robins-I                | Moderate                 |
| Conte et al. 1986            | Robins-I                | Serious                  |
| Adams et al. 1991            | Robins-I                | Serious                  |
| Fracanzani et al. 1995       | Robins-I                | Serious                  |
| McDonnell et al. 1999        | Robins-I                | Serious                  |
| Millman et al. 2001          | Robins-I                | Serious                  |
| Folize et al. 2006           | Robins-I                | Serious                  |
| Phatak et al. 2010           | Robins-I                | Serious                  |
| Harty et al. 2011            | Robins-I                | Serious                  |
| Brissel et al. 2011          | Robins-I                | Serious                  |
| Rehöck et al. 2012           | Robins-I                | Serious                  |
| Rombout-Sestrienkova et al. 2012 | Cochran Risk of Bias     | Poor                     |
| Parra Salinas et al. 2012    | Robins-I                | Serious                  |
| Lukic et al. 2013            | Robins-I                | Serious                  |
| Sundic et al. 2014           | Robins-I                | Fair                     |
| Bardou-Jacquet et al. 2015   | Robins-I                | Moderate                 |
| Koutsavlis et al. 2016       | Robins-I                | Serious                  |
| Brückl et al. 2017           | Robins-I                | Serious                  |
| Ong et al. 2017              | Robins-I                | Serious                  |
| Chayanupatkul et al. 2017    | Robins-I                | Serious                  |
| Jabbour et al. 2018          | Robins-I                | Serious                  |
| Bardou-Jacquet et al. 2019   | Robins-I                | Serious                  |
and 1979 and 58% between 1980 and 1985). A more recent study of patients diagnosed between 1996 and 2010 calculated the SMR as 0.94 (0.71-1.22), indicating that overall survival of HH might not differ from the general population in contemporary cohorts.

Regarding the effects of treatment, a single study reported higher cumulative survival in patients who had been treated compared with those who did not receive treatment (96% vs. 45% at 1 year, 96% vs. 5% at 5 years). Similarly, patients who achieved iron depletion or were treated “adequately” had significantly higher cumulative survival compared with those who did not at 10 years (76% vs. 36%) and at 20 years (40% vs. 4% and 70% vs. 30%), with median survivals of 24 versus 13 years and 16 versus 5 years (Fig. 3).

Analysis of survival based on the intensity of treatment received revealed patients who had received a low or high (over 64) number of venesections had lower overall survival (60% and 70%, respectively) than those in whom between 9 and 63 venesections had been performed (92.5% overall survival). In patients in whom a mild amount of iron had been removed (2-10 g), SMR was low (0.23 [0.08-0.5]), but in patients with over 10 g of iron depleted, mortality was no different than the general population (0.94 [0.71-1.22]).

Finally, several studies have focused on the mortality of patients with HH-related cirrhosis. Five studies investigated the relationship between cirrhosis and mortality in cohorts of patients with HH (n = 1,611 patients). Four of these studies reported that cumulative survival was significantly lower in patients with HH who had cirrhosis compared to those without cirrhosis. The largest of these cohorts reported SMR of all-cause mortality in 1,085 patients with HH, with liver fibrosis 1-2, liver fibrosis 3-4, and cirrhosis (METAVIR scoring system), and found it to be significantly higher in patients with cirrhosis 4.43 (2.53-7.19). The SMR for liver causes of death (37.04 [18.5-66.3]) and deaths from liver cancer (86.1 [37.0-169.5]) were also significantly raised. These data support cirrhosis as being associated with higher mortality in cohorts of HH; however, only one study has investigated whether iron depletion altered survival differences and found no effect.

Together these data suggest that iron depletion therapy may have a positive effect on survival in HH; however, it is impossible to draw firm conclusions, as patient-related and treatment-related confounding factors are not consistently accounted for.

**LIVER CIRRHOSIS, FIBROSIS, AND PORTAL HYPERTENSION**

Liver cirrhosis and its sequelae are well-documented complications of HH, and where present, survival is reduced. Several reports have investigated the relationship between iron overload indices, iron depletion therapy, and the presence of fibrosis and cirrhosis. A paper that evaluated liver biopsies in a HH cohort that included both pediatric and adult patients found that liver fibrosis improved following phlebotomy in all 19 patients who did not have coincident heavy alcohol intake, and that fibrosis was completely reversed in 15 of these 19 subjects. Current evidence also suggests that high serum ferritin levels (> 1,000 μg/L) are associated with an increased risk of cirrhosis and that cirrhosis prevalence is significantly higher among patients with inadequate phlebotomy treatment (93% vs. 68%, P = 0.0002). However, the direction of these associations is unclear, and the evidence is insufficient to infer causality.

Several reports have assessed the effect of iron depletion on the histological appearance of liver cirrhosis or fibrosis by comparing pretreatment and posttreatment
liver biopsy.\textsuperscript{13,17-19} They all found evidence of histological regression of fibrosis following iron depletion in a proportion of patients. The largest and most recent study of treated patients with HH (median follow-up of 9.5 years) reported fibrosis stage improvement in 44 of 106 patients with HH-related F3/4 fibrosis. Fibrosis stage also improved in 23% of the 66 patients in this cohort with cirrhosis at diagnosis. Older age at diagnosis, the presence of diabetes and higher GGT were negatively associated with regression of fibrosis to stage lower than 2.\textsuperscript{17}

Further evidence supporting the benefits of iron depletion in cohorts of cirrhosis includes a study that found overall survival was higher in patients with treated HH cirrhosis than patients with non-HH cirrhosis (75.5% vs. 66.6%), and that only 1 patient with HH cirrhosis had worsening varices during follow-up.\textsuperscript{11} Another study assessed noninvasive markers of fibrosis in patients with HH with moderate iron overload (ferritin 300-1,000 \( \mu \text{g/L} \)) randomized to erythrocytapheresis or sham plasmapheresis.\textsuperscript{20} The mean change in transient elastography (an imaging-based, noninvasive test of liver fibrosis) was similar between both groups following treatment, but the hepascore (a blood-based noninvasive test of liver fibrosis) decreased in the treatment group and increased in the control group (\( P = 0.049 \)).

These data suggest that iron depletion does contribute to regression of fibrosis and cirrhosis in a subset of patients with HH, but further work needs to be done to be able to identify \textit{a priori} which individuals might benefit from treatment and whether reversal of fibrosis stage is associated with clinical benefits including mortality.

\textbf{Hepatocellular Carcinoma}

HCC is a well-recognized complication of HH, including in the absence of cirrhosis, although those with cirrhosis have an up to 200-fold increased risk.\textsuperscript{11}

Four papers (\( n = 538 \)) from Europe and the United States commented on the relationship between HCC and treatment, with differing results. One study reported 11 of 13 (84.6%) HCCs were in livers that were completely depleted of iron,\textsuperscript{13} whereas another found that 80% were from an untreated pool of patients.\textsuperscript{9} Another study found that fibrosis regression was associated with reduced HCC risk (Fig. 4).\textsuperscript{17} However, a recent abstract found no association between successful phlebotomy treatment and risk of HCC (odds ratio [OR] 0.91, 95% CI).\textsuperscript{21}

Overall, although the aim of reducing the risk of HCC often forms part of the rationale for offering treatment, the evidence that phlebotomy has any influence on the development of HCC in hemochromatosis patients is weak.

\textbf{Diabetes}

The prevalence of diabetes in C282Y homozygotes has been decreasing over the past century, largely due to timely diagnosis, with one study reporting a prevalence of 7% in 2008.\textsuperscript{22} In the 2019 UK Biobank study,\textsuperscript{23} including 2890 C282Y homozygotes, only male C282Y homozygotes had a significantly increased rate of type 1 or type 2 diabetes (OR 1.52, 1.18-1.98).

Five included studies (\( n = 554 \)), all cohort, commented on diabetes in hemochromatosis, with four published pre-1986. One study (\( n = 49 \)) analyzed changes in insulin requirements or oral hypoglycemic agent doses before venesection and after venesection in those with idiopathic hemochromatosis and cirrhosis, and found there was no significant difference in 21 patients (43%), a significant reduction in 17 patients (35%), and an increase in the insulin requirement of at least 8 units per day in 8 patients (16%).\textsuperscript{23} Similarly, another noted that the frequency of type 1 diabetes did not significantly differ between adequately and inadequately treated groups.\textsuperscript{12} Conversely, one study found that the clinical features of diabetes improved in 45% of insulin-dependent and 50% of non-insulin-dependent patients with diabetes after biopsy-confirmed iron depletion, although clinical features worsened in 5% and 4%, respectively.\textsuperscript{13} They also commented that the daily dose of insulin decreased in 45% of those undergoing iron depletion.

In general, although it is possible that phlebotomy can reverse diabetes to some extent, the available evidence is scarce and far from conclusive.

\textbf{Cardiovascular Disease}

The prevalence of cardiac failure symptoms in HH has been reported as high as 35%\textsuperscript{15} although in the UK Biobank Study,\textsuperscript{23} C282Y homozygosity was associated with significantly reduced prevalence of coronary artery disease in men but not women.

Four studies commented on cardiovascular disease in hemochromatosis (\( n = 4,033 \)), but only two reported on outcomes following treatment. In a questionnaire study (\( n = 2,851 \), of the 679 patients who complained
of symptoms of heart fluttering, 42 (6.2%) reported an improvement in symptoms following treatment, while 69 (10.1%) reported a worsening of symptoms. The utility of this finding in the context of evaluating the effects of treatment on the heart is questionable, given that the symptom of heart fluttering certainly cannot be assumed to be a manifestation of arrhythmia, and therefore cannot be used as a proxy for underlying cardiovascular disease. A retrospective analysis of death certificates (n = 1,085) found that treated patients with serum ferritin between normal and 1,000 μg/L had a lower cardiovascular mortality than the general population (SMR: 0.27, CI: 0.1-0.5) and, interestingly, these patients did not have a compensatory higher mortality from liver disease.

Clearly, there is very little available evidence on the effects of treatment on cardiovascular disease, particularly that relating to HH-related cardiomyopathy and arrhythmias. Although there are suggestions that treatment can limit cardiovascular mortality, there are too little data to draw any decisive conclusions.

**ADVERSE EVENTS WITH TREATMENT**

There were eight studies (n = 544) that commented on adverse events or side effects associated with treatment of HH. The studies relate to all treatment modalities, with most reporting adverse events being mild in nature.

Studies involving patients undergoing phlebotomy treatment frequently reported side effects including tiredness, fainting, loss of appetite, and needle intolerance in 19%-52% of patients, with tiredness being most frequently reported.

Numerous studies reporting on therapeutic erythrocytapheresis found that up to 25% of collections had complications—mostly light citrate toxicity but also hypotension–related reactions and vein ruptures.

An RCT of therapeutic erythrocytapheresis versus phlebotomy found no significant difference in the number of adverse events per number of procedures (4.7% vs. 1.9%), while a further trial also found little difference
between the two groups, finding procedural discomfort in 19% of their phlebotomy group versus 23% in their erythrocytapheresis group.\(^{(28)}\)

A single study, a phase 1/2 trial of desferasirox, commented on the side effects of iron chelation therapy including diarrhea (49%), headache (27%), and nausea (22%).\(^{(32)}\)

Although common, it appears that most of the adverse events with phlebotomy and erythrocytapheresis are mild. They relate primarily to the effects of hypovolemia, and prehydration is now widely recommended in clinical practice.\(^{(33)}\)

QUALITY OF LIFE AND MENTAL HEALTH

The 2017 HH patient survey, in which nearly 2,000 patients with hemochromatosis from around the world commented on their symptomology, found that symptomatic disease has long been associated with poor quality of life and psychological well-being.\(^{(34)}\)

Three studies (\(n = 2,993\)), of which two were RCTs (\(n = 142\)), provided mixed outcomes. In a survey study of 592 patients with self-reported depression, 242 (40.8%) reported improved symptoms with phlebotomy, while 61 (10.3%) worsened.\(^{(25)}\) The two RCTs, one evaluating perceived health status with phlebotomy versus erythrocytapheresis and another assessing depression in erythrocytapheresis versus sham, found no significant differences.\(^{(20,27)}\)

There are discrepancies within the scant data on the ability of treatment to improve quality of life and mental health, and little to convincingly suggest that treatment has a positive effect.

FATIGUE

Four of the included studies in this paper (\(n = 3,297\)) commented on the effects of treatment on fatigue. One controlled trial found the mean decrease in the Modified Fatigue Impact Scale score was greater in the erythrocytapheresis group compared with sham (mean difference -6.3, 95% CI -11.1 to -1.4, \(P = 0.013\)).\(^{(20)}\) From the cohort studies, one found that weakness/lethargy improved in 51% after iron depletion,\(^{(13)}\) while another found no significant difference in fatigue symptoms when comparing adequately and inadequately phlebotomy-treated groups.\(^{(22)}\) A further study described mixed results, with 54.4% of patients reporting improved symptoms, while 17.2% worsened.\(^{(25)}\)

These data do suggest the possibility that treatment with either phlebotomy or erythrocytapheresis could have a positive impact on symptoms of fatigue.

ARTHRALGIA

Joint pain is the most frequently reported symptom, and both rheumatoid arthritis and osteoarthritis are independently associated with HH.\(^{(23,34)}\)

Seven included studies (\(n = 3,585\)) described arthralgia in hemochromatosis, with a reported improvement in up to 62% of patients following phlebotomy, although one study reported a worsening of arthralgia in 34%.\(^{(13,25,35,36)}\) An RCT found no significant changes to subjective scores of arthralgia following treatment erythrocytapheresis or sham plasmapheresis.\(^{(20)}\)

Although these results suggest a possible role for phlebotomy in arthralgia, a large proportion also report a worsening of their symptoms following treatment, making it difficult to draw any convincing conclusions.

ERECTILE DYSFUNCTION

Sexual health issues are commonly experienced, with a high proportion of men experiencing erectile dysfunction (ED) (39%) and both men (33.5%) and women (58.4%) experiencing loss of libido.\(^{(34)}\)

Four studies (\(n = 3,111\)), all cohort designs focusing on phlebotomy, reported on ED and hypogonadism in HH. They found a reversal of ED symptoms in up to 22% following treatment, although one described a worsening in 27.8%.\(^{10,13,25}\)

Although these limited results demonstrate a possible role for phlebotomy in reversing symptoms of ED, there remains the simultaneous possibility that treatment could exacerbate symptoms.

BIOCHEMICAL MARKERS OF DISEASE SEVERITY AND LIVER FUNCTION TESTS

There is mixed evidence on the utility of liver biochemistry as a screening tool for HH. The high prevalence of abnormal liver biochemistry in patients with HH had highlighted them as a potentially useful screening tool, with clinical studies having found abnormal serum aminotransferase levels in 65%–75%
of patients with HH. Indeed, the incidental finding of abnormal liver function tests (LFTs) is often the catalyst for focused investigation and an early diagnosis of HH. However, more recent evidence paradoxically found that the probability of being a C282Y homozygote increased as the alanine aminotransferase and aspartate aminotransferase activities decreased, possibly reflecting the lack of inflammation induced by iron deposition in HH in comparison with other liver pathologies.

Seven papers (n = 742), including two RCTs and one randomized open-label study, described biochemical markers in HH. One found that both iron and liver indices improved in a greater percentage of adequately treated phlebotomy cohorts, and two further studies found an improvement in LFTs in up to 93% following phlebotomy.

Regarding iron markers, an RCT found that the posttreatment drop in transferrin and transferrin saturation was significant with erythrocytapheresis compared with sham. Similarly, an abstract containing 29 patients reported that the median ferritin reduced from 1,064 mg/L to 421 mg/L in a phlebotomy-treated group and from 597 mg/L to 50 mg/L in an erythrocytapheresis-treated group.

When comparing phlebotomy with erythrocytapheresis, two RCTs reported no significant differences in their effect on iron indices or LFTs.

These results do suggest that both phlebotomy and therapeutic erythrocytapheresis contribute to normalizing iron and liver function indices, presumably through the reduction of iron-mediated oxidative stress on the liver, although it is less clear whether one modality is more effective than the other.

**Discussion**

This is the first review to collate and describe results from studies evaluating the beneficial and harmful outcomes in patients with HH undergoing iron reduction therapy. Iron reduction therapies, with most studies to date focusing on phlebotomy, have been shown to improve outcomes in a variety of domains, although deficiencies in the quality of available evidence makes it difficult to draw meaningful conclusions. Cochrane’s recently attempted network meta-analysis supports this opinion on the strength of current evidence. They found only two randomized clinical trials with usable data, precluding any consequential deductions to be made.

Although phlebotomy is a well-established treatment in HH, its effects have never been conclusively characterized. Ethical restrictions have limited the design of controlled studies, making the true effects of treatment difficult to clarify. While the use of phlebotomy appears largely based on precedent, untangling the available data and developing an evidence base to justify its continued use remains paramount. In our aim to tackle this through this review, we have found that, while there are recurring themes in the available evidence, many discordant results have also been reported.

The Cochrane study found one trial that reported on mortality, finding no deaths in either the phlebotomy or erythrocytapheresis groups over 8 months, and included no studies that reported on mortality beyond 1 year. Conversely, many of the studies included in our review do suggest a survival benefit with venesection, although there are numerous pitfalls in the evidence base.

For example, the confounding effect of initial disease severity was not controlled for in many of the studies. The studies that demonstrated those requiring a high number of venesection procedures to achieve iron depletion had a higher mortality rate, possibly represented a population with severe iron loading. Similarly, the observed high mortality rate in those who underwent very few treatment procedures perhaps represented those with advanced or refractory disease at the time of diagnosis. This is supported by the fact that the average follow-up time within the quartile receiving the fewest number of venesections was 1 year (all died), compared with 11 years in the quartile receiving the highest number (5 of 12 died). Conversely, another study found that patients necessitating low amounts of iron removal by phlebotomy had lower overall mortality than the general population, although this subgroup may display a milder disease phenotype. One study found that survival was significantly better in those with “adequate” treatment (i.e., those who had received frequent phlebotomy and responded biochemically). However, the “inadequate” group included those with advanced or refractory disease, including those who did indeed receive venesection but did not respond. Finally, it is worth noting that two studies included patients who were diagnosed before...
the availability of HFE testing; therefore, their cohorts would likely include not only patients with non-HFE hemochromatosis, but a higher proportion with late-presenting, severe phenotypes. As a further example of suboptimal controlling, another study compared patients with HH to a diverse control group consisting of those with differing liver pathologies and varying treatment statuses. 

Despite the weaknesses in the evidence, these findings do appear to suggest that phlebotomy improves mortality, but particularly in those who show a biochemical response to treatment and achieve iron depletion within a reasonable time frame.

With regard to liver fibrosis, while phlebotomy appears capable of reversing pathology, the evidence is limited. While two studies suggested a degree of reversibility with phlebotomy, further supportive data come from abstracts only. Similarly, an RCT described a reduction in markers of fibrosis with treatment erythrocytapheresis, but it must be noted that there was no fibrosis in the cohort at baseline.

Regarding liver cirrhosis, one study reported a higher frequency of cirrhosis in patients inadequately treated with phlebotomy. However, adequate treatment could feasibly be precluded by the presence of cirrhosis itself, and therefore cannot simply be attributed to the effects of phlebotomy.

One study’s finding that all cases of HCC were found in cirrhotic livers, and remarkably most in those that were depleted of iron, may suggest that phlebotomy does not prevent HCC in the cirrhotic stage. However, the fact that those with HCC were found to have the highest amounts of mobilizable iron may paradoxically suggest a role for phlebotomy. Similarly, it is accepted that those with high serum ferritin at diagnosis are at a greater risk of HCC. Moreover, another paper found that the vast majority of HCC cases were from the untreated pool of patients.

As with Cochrane’s study, we found no serious adverse events in those receiving phlebotomy or erythrocytapheresis, while there was also no significant improvement in health-related quality of life with either modality.

Our findings on the effects of treatment on extrahepatic manifestations, however, are contradictory and sparse. There were discrepancies in the outcomes with regard to diabetes, cardiac symptoms and function, mental health, fatigue, ED, and arthralgia. For example, interpretation of the already conflicting reports on the effects of iron reduction therapy on joint pain is further limited by the heterogeneous nature of the included cohorts, especially given the variety of arthritic phenotypes in HH.

The discrepancy in outcomes points toward a lack of robust evidence, with many contributing factors. The relevant studies are primarily retrospective cohort studies, with small numbers participating, and are largely unmatched for the presence of cirrhosis, comorbidities, or co-interventions. Nineteen of the 21 (90%) included nonrandomized studies of intervention had a serious risk of bias when analyzed with the ROBINS-I tool, and many of the studies used nonstandardized treatment regimens that varied within studies, let alone between studies, which is especially significant given that iron reduction therapy is not standardized. Furthermore, much of the data on the effects of treatment come from retrospective questionnaires, which are weakened by heavy recall and selection biases.

A further pitfall potentially affecting a significant portion of the studies, as they were performed before the introduction of HFE testing, is the probability of secondary iron overload cases being diagnosed as HH. The HFE gene was identified as recently as 1996, with homozygosity for a missense mutation in this gene being responsible for most cases of HH. Since this point, the diagnosis of HH has largely been defined genetically, whereby, prior to this, there was a greater emphasis on phenotype. Given that a significant proportion of the cohorts across many of the included studies were diagnosed before the discovery of HFE, there is the probability that cases of secondary iron overload were erroneously diagnosed as HH. This is especially probable given that cirrhosis with secondary iron overload is far more common than cirrhosis secondary to HH, and that the two are indistinguishable histologically. These phenomena have likely introduced a bias to reported outcomes in these earlier papers and so must be interpreted cautiously in the context of confirmed HH.

Another noteworthy caveat to the available evidence is the high prevalence of advanced liver disease in many of the included, and particularly earlier, studies. Up to 85% of study participants were known to have cirrhosis in one study, warranting caution when applying findings to a more generally representative HH population with milder disease. Even with inherent selection bias, studies estimate the prevalence of biopsy-proven cirrhosis to be 23%-28% in Caucasians with HH, with most of these also having co-existing...
Cirrhosis solely due to the effects of iron overload was seen in only 3%. It has also been reported that the lifetime incidence of severe liver disease alone appears to be approximately 9% of male HFE C282Y homozygotes of European ancestry, based on data from prospective cohort studies. (45) Thus, our findings on the efficacy of treatment possibly have less relevance in those with less advanced disease, which is important given that these patients are far more prevalent in clinical practice.

Overall, the positive data outlined in this review, although limited, do suggest a benefit of treatment, which may be multifaceted (Fig. 5). The dearth of robust evidence is unlikely to change in the near future, until and when new therapies that challenge phlebotomy as the gold standard emerge. Indeed, hepcidin agonists are on the horizon for HH, (46) and the related clinical trials will provide informative evidence for clinical practice, regardless of the outcomes. For now, phlebotomy remains the mainstay of treatment for HH and will continue to be recommended, given the potential benefits, even in the absence of iron-clad evidence supporting its use.

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